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(54) Identification and use of molecules implicated in pain

(57) The invention relates to the use of:

(a) an isolated gene sequence that is down-regulated in the spinal cord of a mammal in response to mechanistically distinct first and second models of neuropathic or central sensitization pain;
(b) an isolated gene sequence comprising a nucleic acid sequence of any of Tables I to VI;
(c) an isolated gene sequence having at least 80% sequence identity with a nucleic acid sequence of any of Tables I to VI;
(d) an isolated nucleic acid sequence that is hybridizable to any of the gene sequences according to (a), (b) or (c) under stringent hybridisation conditions;
(e) a recombinant vector comprising a gene sequence or nucleic acid sequence according to any one of (a) to (d);
(f) a host cell containing the vector according to (e);
(g) a non-human animal having in its genome an introduced gene sequence or nucleic acid sequence or a removed or down-regulated gene sequence or nucleic acid sequence according to any one of (a) to (d);
(h) an isolated polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence encoded by a nucleotide sequence according to any one of (a) to (d), or a variant polypeptide thereof with sequential amino acid deletions from the C terminus and/or the N-terminus;
(i) an isolated polypeptide encoded by a nucleotide sequence according to any one of (a) to (d); or
(j) an isolated antibody that binds specifically to a polypeptide according to (h) or (i);

in the screening of compounds for the treatment of pain, or for the diagnosis of pain.

The invention also relates to the use of naturally occurring compounds such as peptide ligands of the expression products of the above gene sequences and their associated signal transduction pathways for use in the treatment of pain.

EP 1 284 298 A2

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to nucleic acids, their expression products and pathways involved in pain, and their use in screening for molecules that can alleviate pain. The invention further relates to methods for the assay and diagnosis of pain in patients.

BACKGROUND TO THE INVENTION

[0002] Pain is currently classified into four general types. Post-operative acute pain can be successfully treated with existing pain medications of e.g. the opioid and non-steroidal anti-inflammatory (NSAID) types, and is usually short-term and self-limiting. A second type of pain, present e.g. in cancer and arthritis, is also responsive to medication initially with a NSAID and in its later stages with opioids. Neuropathic pain arises from damage to the central or peripheral nerve systems, and is more effectively treated with antidepressants or anticonvulsants. A fourth type of pain called central sensitization results from changes in the central nervous system as a result of chronic pain, these changes often being irreversible and difficult to treat. Nerve pain from shingles or diabetes falls into this and the neuropathic category. Changes occur where pain is at first poorly controlled and gradually progress to the point where a person is sensitive to stimuli which would not normally cause pain, for example a light touch. People with pain of this kind often describe a widening of the pain area to include areas which had originally not been injured or which were thought not to be involved in pain. This classification is, however based on clinical symptoms rather than on the underlying pain mechanisms.

[0003] Opiates such as morphine belong to a traditional class of pain-relieving compounds that are now recognized as binding to opiate receptors. Naturally occurring polypeptides have also been found to have opiate-like effects on the central nervous system, and these include β-endorphin, met-enkephalin and leu-enkephalin.

[0004] Salicin was isolated at the beginning of the 19th century, and from that discovery a number of NSAIDs such as aspirin, paracetamol, ibuprofen, flurbiprofen and naproxen were developed. NSAIDs are by far the most widely used pain-relieving compounds, but can exhibit side effects, in particular irritation of the GI tract that can lead to the formation of ulcers, gastrointestinal bleeding and anemia.

[0005] Interest in the neurobiology of pain is developing: see a colloquium sponsored by the US National Academy of Sciences in December 1998 concerning the neurobiology of pain and reviewed in *The Scientist* **13[1]**, 12, 1999. Many pain mechanisms were discussed including the role of the capsaicin receptors in pain, (M.J. Caterina *et al.*, *Nature,* **389**, 816-824, 1997). Large dosages of capsaicin were reported to disable that receptor, (W.R. Robbins *et al.*, *Anesthesia and Analgesia*, **86**, 579-583, 1998). Additionally, a tetrodotoxin-resistant sodium channel found in small diameter pain-sensing neurons (PN3) was discussed (A.N. Akopian *et al.*, *Nature,* **379**, 257-262, 1986) and L. Sangameswaran *et al.*, *Journal of Biological Chemistry,* **271**, 953-956, 1996). Its involvement in transmission and sensitization to pain signals has been reported, (S.D. Novakovic *et al.*, *Journal of Neuroscience,* **18**, 2174-2187, 1998). A further tetrodotoxin-resistant sodium channel has been reported (S. Tate *et al.*, *Nature Neuroscience,* **1**, 653-655 1998).

[0006] Second messenger systems have also been shown to be important since knockout-mice lacking protein kinase C (PKC) γ were reported to respond to acute pain e.g. from a hot surface, but not to respond to neuropathic pain when their spinal nerves are injured (Malmberg *et al.*, *Science,* **278**, 279-283 (1997).

[0007] Present methods for identifying novel compounds that relieve pain of one or more of the types indicated above suffer from the defect that they are dependent either on the relatively limited number of receptors known to be involved in pain or on the empirical identification of new receptors which is an uncertain process. In relation to known receptors, for example the opioid receptor, research directed to improved compounds offers the possibility of screenining compounds that have a better therapeutic ratio and fewer side effects. This does not lead naturally to compounds for different pain receptors that have new modes of action and new and qualitatively different benefits. Even when newly identified additional receptors are taken into account, known receptors revolve around tens of gene products. However, there are between 30,000 and 40,000 genes in the genome of an animal and more of them are concerned with nervous system function than with peripheral function. We therefore concluded that a large number of receptors and pathways are important to the transduction of pain, but up to now have remained unknown.

SUMMARY OF THE INVENTION

[0008] It is an object of the invention to provide sequences of genetic material for which no role in pain has previously been disclosed, and which are useful, for example, in:

- identifying metabolic pathways for the transduction of pain

- identifying from said metabolic pathways compounds having utility in the diagnosis or treatment of pain
- producing proteins and polypeptides with a role in the transduction of pain;
- producing genetically modified non-human animals that are useful in the screening of compounds having utility in the treatment or diagnosis of pain.
- Identifying ligand molecules for receptors involved in said metabolic pathways and having utility in the treatment of pain.

[0009] It is yet a further object of the invention to provide research tools, for example non-human animals and microorganisms, that can be used in screening compounds for pharmacological activity, especially pain-reducing activity.

[0010] The present invention is based on sequences that are down-regulated in two models of chronic pain, namely streptozocin-induced diabetes and chronic constrictive injury (CCI) to a nerve leading to the spine, for example the sciatic nerve.

[0011] In one aspect, the invention relates to the use in the screening of compounds that are effective in the treatment of pain, or in the diagnosis of pain, of:

(a) an isolated gene sequence that is down regulated in the spinal cord of a mammal in response to first and second models of pain, for example in response to streptozocin-induced diabetes and in response to a chronic constrictive injury to a nerve leading into the spine;
(b) an isolated gene sequence having at least 80% sequence identity with any of the nucleic acid sequences of Tables I - VI, preferably 85% sequence identity, more preferably 90%, increasingly preferably 95%, most preferably 99%.
(c) an isolated nucleic acid sequence comprising a sequence that is hybridizable to any of the gene sequences according to (a) or (b) under stringent hybridisation conditions;
(d) a recombinant vector comprising any of the gene sequences according to (a) to (c);
(e) a host cell containing the vector according to (d);
(f) a non-human animal, for use in the screening of compounds that are effective in the treatment of pain, or in the diagnosis of pain, having in its genome an introduced gene sequence or a removed or down-regulated nucleotide sequence, said sequence becoming down-regulated in the spinal cord of a mammal in response to first and second models of pain, particularly neuropathic or sensitisation pain, for example in response to streptozocin-induced diabetes and in response to a chronic constrictive injury to a nerve leading into the spine;
(g) an isolated polypeptide containing an amino acid sequence at least 90% identical to an amino acid sequence encoded by a nucleotide sequence according to any one of (a) to (d), or a variant thereof with sequential amino acid deletions from the C terminus and/or the N-terminus; or
(h) an isolated antibody that binds specifically to the isolated polypeptide according to (g).

[0012] The invention further provides a compound that is useful in the treatment or diagnosis of pain and that modulates the action of an expression product of a gene sequence that becomes down-regulated in the spinal cord of a mammal in response to first and second models of pain, for example being down-regulated both in response to streptozocin induced diabetes and in response to chronic constrictive injury to a nerve leading into the spine.

[0013] The invention also relates to the use of naturally occurring compounds such as peptide ligands of the expression products of the above gene sequences and their associated signal transduction pathways for the treatment of pain.

DESCRIPTION OF PREFERRED EMBODIMENTS

DEFINITIONS

[0014] Within the context of the present invention:

- "Comprising" means consisting of or including. Thus nucleic acid comprising a defined sequence includes nucleic acid that may contain a full-length gene or full-length cDNA. The gene may include any of the naturally occurring regulatory sequence(s), such as a transcription and translation start site, a promoter, a TATA box in the case of eukaryotes, and transcriptional and translational stop sites. Further, nucleic acid comprising a cDNA or gene may include any appropriate regulatory sequences for the efficient expression thereof *in vitro*.

- "Isolated" requires that the material be removed from its original environment (e.g. the natural environment if it is naturally occurring). For example, a naturally occurring polynucleotide or a peptide present in a living animal is not isolated, but the same polynucleotide or peptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotide can be part of a vector and/or such polynucleotide or peptide can

be part of a composition, and still be isolated in that the vector or composition is not a part of its natural environment.

- "Mechanistically distinct" in relation to pain models implies that the pain is induced by mechanisms that differ in kind rather than being variants of a similar pain model. Thus diabetic pain and chronic constrictive pain models are mechanistically distinct, whereas spinal nerve ligation models and sciatic nerve ligation models which both work by ligation are not.

- "Purified" does not require absolute purity; instead it is intended as a relative definition. Purification of starting materials or natural materials from their native environment to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

- "Nucleic acid sequence" or "gene sequence" means a sequence of nucleotides or any variant or homologue thereof, or truncated or extended sequence thereof, and is preferably indicated by a Genebank accession number. Also within the scope of the present invention are down-regulated nucleic acid sequences which encode expression products which are components of signaling pathways. This invention also includes any variant or homologue or truncated or extended sequence of the down-regulated nucleotide sequence. Also within the scope of the present invention, the term "nucleic acid(s) product", or "expression product" or "gene product" or a combination of these terms refers without being biased, to any, protein(s), polypeptide(s), peptide(s) or fragment(s) encoded by the down-regulated nucleotide sequence.

- "Operably linked" refers to a linkage of polynucleotide elements in a functional relationship. For instance, a promoter or an enhancer is operably linked to a coding sequence if it regulates the transcription of the coding sequence. In particular, two DNA molecules (such as a polynucleotide containing a promoter region, and a polynucleotide encoding a desired polypeptide) are said to be "operably linked" if the nature of the linkage between the two polynucleotides does not (1) result in the introduction of a frame-shift mutation and (2) interfere with the ability of the polynucleotide containing the promoter to direct the transcription of the coding polynucleotide.

  "Gene product" refers to polypeptide - which is interchangeable with the term protein - which is encoded by a nucleotide sequence and includes single-chain polypeptide molecules as well as multiple-polypeptide complexes where individual constituent polypeptides are linked by covalent or non-covalent means. Polypeptides of the present invention may be produced by synthetic means (e.g. as described by Geysen *et al.*, 1996) or by recombinant means.

  The terms "variant", "homologue", "fragment", "analogue" or "derivative" in relation to the amino acid sequence for the polypeptide of the present invention includes any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) amino acid from or to the sequence providing the resultant polypeptide has the native gene product activity. In particular, the term "homologue" covers homology with respect to structure and/or function. With respect to sequence homology, there is at least 90%, more preferably at least 95% homology to an amino acid sequence encoded by the relevant nucleotide sequence shown in Tables I - VI, preferably there is at least 98% homology.

  Typically, for the variant, homologue or fragment of the present invention, the types of amino acid substitutions that could be made should maintain the hydrophobicity/hydrophilicity of the amino acid sequence. Amino acid substitutions may include the use of non-naturally occurring amino acid analogues.

  In addition, or in the alternative, the protein itself could be produced using chemical methods to synthesize a polypeptide, in whole or in part. For example, peptides can be synthesized by solid phase techniques, cleaved from the resin, and purified by preparative high performance liquid chromatography (e.g. Creighton (1983) Proteins Structures and Molecular Principles, WH Freeman and Co., New York, NY, USA). The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (e.g. the Edman degradation procedure).

  Direct peptide synthesis can be performed using various solid-phase techniques (Roberge JY *et al* Science Vol 269 1995 202-204) and automated synthesis may be achieved, for example, using the ABI 431 A Peptide Synthesizer (Perkin Elmer) in accordance with the instructions provided by the manufacturer. Additionally, the amino acid sequence of a gene product, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with a sequence from other subunits, or any part thereof, to produce a variant polypeptide.

  In another embodiment of the invention, a gene product natural, modified or recombinant amino acid sequence may be ligated to a heterologous sequence to encode a fusion protein. For example, for screening of libraries for compounds and peptide agonists and antagonists of gene product activity, it may be useful to encode a chimeric gene product expressing a heterologous epitope that is recognised by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between a gene product sequence and the heterologous protein sequence, so that the gene product may be cleaved and purified away from the heterologous moiety.

The gene product may also be expressed as a recombinant protein with one or more additional polypeptide domains added to facilitate protein purification. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilised metals (Porath J, Protein Expr Purif Vol 3 1992 p263-281), protein A domains that allow purification on immobilised immunoglobulin, and the domain utilised in the FLAGS extension/affinity purification system (Immunex Corp, Seattle, WA, USA). The inclusion of a cleavable linker sequence such as Factor XA or enterokinase (Invitrogen, San Diego, CA, USA) between the purification domain and the gene product is useful to facilitate purification.

- "Pain" includes chronic pain, neuropathic pain, pain arising from central sensitisation, and in particular diabetic pain.

- "Stringent hybridization conditions" is a recognized term in the art and for a given nucleic acid sequence refers to those conditions which permit hybridization of that sequence to its complementary sequence and closely homologous sequences. Conditions of high stringency may be illustrated in relation to filter-bound DNA as for example 2X SSC, 65°C (where SSC = 0.15M sodium chloride, 0.015M sodium citrate, pH 7.2), or as 0.5M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS), 1mM EDTA, at 65°C, and washing in 0.1xSCC/0.1% SDS at 68°C (Ausubel F.M. *et al.*, eds, 1989, *Current Protocols in Molecular Biology,* Vol. I, Green Publishing Associates, Inc., and John Wiley & Sons Inc., New York, at p. 2. 10.3). Hybridization conditions can be rendered highly stringent by raising the temperature and/or by the addition of increasing amounts of formamide, to destabilize the hybrid duplex of non-homologous nucleic acid sequence relative to homologous and closely homologous nucleic acid sequences. Thus, particular hybridisation conditions can be readily manipulated, and will generally be chosen depending on the desired results.

- "Variants or homologues" include (a) sequence variations of naturally existing gene(s) resulting from polymorphism (s), mutation(s), or other alteration(s) as compared to the above identified sequences, and which do not deprive the encoded protein of function (b) recombinant DNA molecules, such as cDNA molecules encoding genes indicated by the relevant Genebank accession numbers and (c) any sequence that hybridizes with the above nucleic acids under stringent conditions and encodes a functional protein or fragment thereof.

IDENTIFIED SEQUENCES

[0015] The inventors have identified nucleotide sequences that give rise to expression products listed in Tables I - VI, that become differentially expressed in the spinal cord in response to two distinct chronic pain stimuli, for example neuropathic and/or central sensitization pain stimuli, and that are believed to be involved in the transduction of pain. In Tables I - VI, * denotes more preferred nucleic acid sequences and ** denotes most preferred nucleic acid sequences. These nucleic acid sequences have not previously been implicated in the transduction of pain.

[0016] The validity of the present experimental procedure was confirmed by the fact that nucleotide sequences were obtained as a result of the investigation whose function in the transduction of pain has been previously confirmed and established. These nucleic acid sequences are not part of this invention. Any of the nucleic acid sequences and expression products can be used to develop screening technologies for the identification of novel molecules for the prevention or treatment of pain. These screening technologies could also be used to ascribe new pain therapeutic indications to molecules that have not previously been identified as being useful for the prevention or treatment of pain. Furthermore, the said nucleic acid sequences can be used as diagnostic tools and for the development of diagnostic tools.

Table I -

Sequences whose expression products are kinases					
Expression productor name (Reference)	**Rat Accession Number**	**Mouse accession number**	**Human Accession Number**	**Reaction**	**Assay**
Pyruvate kinase, M1 and M2 subunit s (Refs :1 - 2)	M24359 (SEQ ID No's 1-3)	X97047	X56494	Tissue-specific promoter; Carbohydrate kinase	Kinase

Table II -

Sequences whose expression products are receptors					
Expression Product or Name (Reference)	**Rat Accession Number**	**Mouse accession Number**	**Human Accession Number**	**Reaction**	**Assay**
Dopamine receptor D.sub. 1** (Ref : 3)	I58000 (SEQ ID NO 4)			Dopamine receptor	Receptor
Putative GABA-B1a receptor** (Ref : 4)		AF114168 (SEQ ID No's 5-6)		GABA-B Receptor	Receptor

Table III -

Sequences whose expression products are transporters					
Expression Product or Name	**Rat Accession Number**	**Mouse Accession Number**	**Human Accession Number**	**Reaction**	**Assay**
Differentiation-associated Na-dependent inorganic phosphate cotransporter (Ref : N/A)	AF271235(SEQ ID NO's 7-8)			Trans-membrane phosphate transport	Transporter
Putative vacuolar assembly protein VSP41 gene (Ref : N/A)	U87309		AAM47563. 1 (SEQ ID No 9)	Vacuolar assembly and traffic	Transporter

Table IV -

Sequences whose expression products are G-protein coupled receptor proteins					
Expression product or Name	**Rat Accession Number**	**Mouse Accession Number**	**Human Accession Number**	**Function**	**Assay**
Git1 (G-protein-coupled receptor kinase-interactor 1 ; GPCR kinase-associated ADP-ribosylation factor) (Ref : 5)	AF085693 (SEQ ID NO 10-11)			Regulation of activity of ARF6 in phosphatidyl-inisitol 3-kinase signalling pathways ; β2 adrenergic receptor regulation	Ligand binding

Table V -

Sequences whose expression products are DNA-binding proteins					
Expression Product or Name	**Rat Accession Number**	**Mouse Accession Number**	**Human Accession Number**	**Reaction**	**Assay**
Putative histone H3.3A (Ref: 6)		X91866	M11354(SEQ ID NO 12-13)	DNA binding	DNA binding

Table VI -

Sequences whose expression products are other enzymes					
Expression product or Name	**Rat Accession Number**	**Mouse Accession Number**	**Human Accession Number**	**Reaction**	**Assay**
3-Hydroxy 3-methylglutaryl coenzyme A synthase, cytosolic * (Ref: 7)	X52625 (SEQ ID No's 14-15)			Cholesterol biosynthesis	Ligase
Acyl-CoA synthetase II, brain (Ref : N/A)	D360666 (N/A)			Fatty acid metabolism	Ligase
Farnesyl diphosphate synthase ** (Ref : 8)	M34477 (Seq ID No's 16-17)			Isoprene biosynthesis	Ligase
Bendless protein (Ref : N /A)	AB032739 (Seq ID No's 18-19)		E12457	Protein degradation	Ligase
fatty acid synthase (Ref: 9)	X62888 (SEQ ID No's 20-21)			Fatty acid synthesis	Ligase
Glutamine synthetase (EC 6.3.1.2) ** (Ref : 10)	M91652 (SEQ ID NO's 22-23)			Amino acid metabolism	Ligase
Putative seryl-tRNA synthetase (Ref No : 11)			X91257 (SEQ ID NO's 24-25)	Ligase	Ligase
Enolase, alpha alpha, non-neuronal (NNE) (REF NO 12)	X02610	X52379	M14328 (SEQ ID NO's 26-27)	Glycolysis	Lyase
Aldose reductase, lens (AREC 11.1.21) (REF : 13)	X05884 (SEQ ID NO's 28-29)			Reduces carbonyl	Oxidoreductase
Cytochrome-c oxidase I, mitochondrial (Ref : 14)	S79304 (SEQ ID NO's 30-31)			Mitochrondrial energy metabloism	Oxidoreductase

Table VI - (continued)

Sequences whose expression products are other enzymes					
Expression product or Name	**Rat Accession Number**	**Mouse Accession Number**	**Human Accession Number**	**Reaction**	**Assay**
Lactate dehydrogenase-B (LDH-B) (Ref : 15)	U07181 (SEQ ID NO's 32-33)	X51905	Y00711	Glycolysis	Oxidoreductase
Putative cytochrome c oxidase VIB (EC 1.9.3.1) (Ref : 16)			X13923 (SEQ ID NO's 34-35)	Mitochrondrial energy metabolism	Oxidoreductase
Putative NADH: ubiquinone oxidoreductasePG IV subunit (Ref : 17)			AF044953 (SEQ ID No's 36-37)	Mitochrondrial energy metabolism	Oxidoreductase
Putative succinate dehydrogenase flavoprotein (Ref: N/A)		AF095938 (SEQ ID No's 38-39)	AF171022	TCA cycle	Oxidoreductase
Putative ubiquinol-cytochrome-c reductase (EC 1.10.2.2) core protein II (REF: 18)			J04973 (SEQ ID No's 40-41)	Mitochrondrial energy metabolism	Oxidoreductase
Stearoyl-coA desaturase 2 * (Ref: N/A)	AB032243 (SEQ ID N0's 42-43)	M26270		Fatty acid biosynthesis	Oxidoreductase
Ribophorin I * (Ref: 19)	X05300 (SEQ ID No's 44-45)			Glycosolation	Transferase
Sulfotransferase-like protein (REF : 20)	AF188699 (SEQ ID No's 46-47)			Transferase	Transferase
ATP synthase, H+, alpha subunit, mitochondrial (EC 3.6.1.34) (Ref: N/A)	X56133 (SEQ ID No's 48-49)			Mitochrondrial energy metabolism	Hydrolase
F1F0 ATPase delta subunit (REF : 21)	U00926 (SEQ ID No's 50-51)			Mitochrondrial energy metabolism	Hydrolase
Putative dihydropyrimidinase related protein * (REF: 22)			D78013 (SEQ ID NO's 52-53)	Pyrimidine degradation	Hydrolase
Heat shock protein 90 (REF : 23)	S45392 (SEQ ID NO's 114-115)	M18186	M16660	Cell protection	Hydrolase

Table VI - (continued)

Sequences whose expression products are other enzymes					
Expression product or Name	**Rat Accession Number**	**Mouse Accession Number**	**Human Accession Number**	**Reaction**	**Assay**
Myelin basic protein S (MBP S) (REF :24)	K00512 SEQ ID No 54)			Myelin structural protein	Ligand binding
Transferrin (Ref 25)	D38380 (SEQ ID No's 55-56)			Iron transport	Ligand binding
Neurofilament, light molecular weight (NF-L) (Ref : 26)	AF031880 (SEQ ID No's 57-58)			Cytoskeleton	Ligand binding
Myelin-associayted glycoprotein (MAG) (Ref : 27)	M1680 (SEQ ID NO's 59-60)	M31811		Cell adhesion molecule for postnatal neural development	Ligand binding
NF-M middle molecular weight neurofilament protein (Ref : 28)	M18628 (SEQ ID No's 61-62)			Cytoskeleton	Ligand binding
Neuro-degeneration associated-protein 1 (Ref: 29)	D32249 (SEQ ID No's 63-64)			Protein sorting; synaptic communication and plasticity	Ligand binding
S-100 protein β-subunit (REF: 30)	X01090 (SEQ ID No 65)			Zinc and calcium binding	Ligand binding
Microtubule-associated protein 1b (Map 1b) (Ref: 31)	X60370 (SEQ ID No's 66-67)		L06237	Cytoskeleton protein, neuronal growth/ regeneration; microtubule binding protein	Ligand binding
Putative cdc 37 homolog (Ref: 32)	D26564 (Seq ID No's 68-69)			Cell signalling ; cell cycle protein	Ligand binding
Putative ras-related protein Rab-5c (Ref : 33)			U11293 (SEQ ID No's 70-71)	Small GTP binding protein	Ligand binding
Putative gelsolin (Ref: 34)		J04953 (SEQ ID No's 72-73)		Cytoskeleton protein	Ligand binding
Cd81 antigen (target of antiproliferative antibody 1) (Ref : 35)	U19894 (SEQ ID No's 74-75)	X59047	M33680	Regulator for neuron-induced astrocyte differentiation; microglial effector functions	Ligand binding

Table VI - (continued)

Sequences whose expression products are other enzymes					
Expression product or Name	**Rat Accession Number**	**Mouse Accession Number**	**Human Accession Number**	**Reaction**	**Assay**
Mobp81 (Myelin-associated/Oligo-dendrocytic basic protein 81) (Ref : 36)	X87900 (SEQ ID No's 76-77)			Myelin compaction	Ligand binding
Syntaxin binding protein n-sec1, sec1 homolog (Ref : N/A)			BC002869 (Seq ID No's 78-79)	Neuro-transmission	Ligand binding
Alpha-internexin (Ref: 37)	M73049 (SEQ ID No's 80-81)			Cytoskeleton protein; neuronal intermediate filament that can self-assemble	Ligand binding
Putative β-sarcoglycan A3b (Ref: N/a)		AB024921 (SEQ ID No's 82-83)		Cytoskeleton protein	Ligand binding
CGI-78 protein Ref: 38)	AF151835		AF151835(SEQ ID No's 84-85)	Unknown	Ligand binding
KIAA0143 (Ref: 39)			D63477 (SEQ ID NO's 86-87)	Transmembrane protein	Ligand binding
Septin 2 (KIAA0128 ; Ref 39)			D50918 (SEQ ID No's 88-89)	GTPase; cytokinesis	Ligand binding
Nucleobindin (Ref: 40)	Z36277 (SEQ ID No's 90-91)			Unknown	Ligand binding
Myelin protein SR13 (Ref: 41)	M69139 (SEQ ID NO's 92-93)	S55427		Myelin structural protein	Ligand binding
B-Actin, cytoplasmic (Ref: 42)	V01217 (SEQ ID NO's 94-95)	X03672		Structural protein	Ligand binding
Ly6/neurotoxin (Lynx1) homolog (Ref: 43)		AF141377 (SEQ ID No's 96-97)		Neuro-transmitter modulator	Ligand binding
Astrocytic phosphoprotein; PFA 15 gene (Ref: N/A)	AJ243949 (SEQ ID NO's 98-99)	X86694		PKC substrate	Ligand binding
PLIC-1 (Ref: N/A)		AF177345 (SEQ ID NO 100-101)		Cytoskeleton interaction	Ligand binding
Nfx1 (tip associating protein (TAP) gene) (Ref: N/A)	AF093139 (SEQ ID NO's 102-103)	AF093140		Unknown	Logand binding

Table VI - (continued)

Sequences whose expression products are other enzymes					
Expression product or Name	**Rat Accession Number**	**Mouse Accession Number**	**Human Accession Number**	**Reaction**	**Assay**
Alpha-Crystallin B (Ref N/A)	U04320 SEQ ID NO's 104-105)	M73741	M28638	Stress response ; heat shock element	Ligand binding
Heat shock-like protein 70 kD (Ref : 44)	X70065 (SEQ ID No's 106-107)	U73744	Y00371	Stress response	Ligand binding
Tau microtubule-associated protein (Ref : 45)	X79321 (SEQ ID NO's 108-109)			Microtubule associated protein expressed in neurons	Ligand binding
Myelin, Schwann cell, Peripheral (P-0) (Ref : 46)	K03242 (SEQ ID No's 110-111)			Myelin structural protein	Ligand binding
B-Tubulin class 1 (Ref: 47)	AB011679 (SEQ ID NO's 112-113)	X04663	AF14139	Structural protein	Ligand binding
Putative ribonuclease III (Ref : N/A)			AF116910 (SEQ ID NO's 116-117)	RNA hydrolysis	Hydrolase

PRODUCTION OF POLYPEPTIDES AND NUCLEIC ACIDS

Vectors

[0017] Recombinant expression vectors comprising a nucleic acid can be employed to express any of the nucleic acid sequences of the invention. The expression products derived from such vector constructs can be used to develop screening technologies for the identification of molecules that can be used to prevent or treat pain, and in the development of diagnostic tools for the identification and characterization of pain. The expression vectors may also be used for constructing transgenic non-human animals.

[0018] Gene expression requires that appropriate signals be provided in the vectors, said signals including various regulatory elements such as enhancers/promoters from viral and/or mammalian sources that drive expression of the genes or nucleic acid sequences of interest in host cells. The regulatory sequences of the expression vectors used in the invention are operably linked to the nucleic acid sequence encoding the pain-associated protein of interest or a peptide fragment thereof.

[0019] Generally, recombinant expression vectors include origins of replication, selectable markers, and a promoter derived from a highly expressed gene to direct transcription of a downstream nucleoide sequence. The heterologous nucleotide sequence is assembled in an appropriate frame with the translation, initiation and termination sequences, and if applicable a leader sequence to direct the expression product into the periplasmic space, the extra-cellular medium or cell membrane.

[0020] In a specific embodiment wherein the vector is adapted for expressing desired sequences in mammalian host cells, preferred vectors will comprise an origin of replication from the desired host, a suitable promoter and an enhancer, and also any necessary ribosome binding sites, polyadenylation site, transcriptional termination sequences, and optionally 5'-flanking non-transcribed sequences. DNA sequences derived from the SV40 or CMV viral genomes, for example SV40 or CMV origin, early promoters, enhancers, and polyadenylation sites may be used to provide the required non-transcribed genetic elements.

[0021] A recombinant expression vector used in the invention advantageously also comprises an untranscribed poly-

nucleotide region located at the 3'end of the coding sequence (ORF), this 3'-UTR (untranslated region) polynucleotide being useful for stabilizing the corresponding mRNA or for increasing the expression rate of the vector insert if this 3'-UTR harbours regulation signal elements such as enhancer sequences.

[0022] Suitable promoter regions used in the expression vectors are chosen taking into account the host cell in which the nucleic acid sequence is to be expressed. A suitable promoter may be heterologous with respect to the nucleic acid sequence for which it controls the expression, or alternatively can be endogenous to the native polynucleotide containing the coding sequence to be expressed. Additionally, the promoter is generally heterologous with respect to the recombinant vector sequences within which the construct promoter/coding sequence has been inserted. Preferred promoters are the LacI, LacZ, T3 or T7 bacteriophage RNA polymerase promoters, the lambda PR, PL and Trp promoters (see EP-0 036 776), the polyhedrin promoter, or the p10 protein promoter from *baculovirus* (kit Novagen; Smith *et al.*, (1983); O'Reilly *et al.* (1992)).

[0023] Preferred selectable marker genes contained in the expression recombinant vectors used in the invention for selection of transformed host cells are preferably dehydrofolate reductase or neomycin resistance for eukaryotic cell culture, TRP1 for *S. cerevisiae* or tetracycline, rifampicin or ampicillin resistance in *E. coli,* or Levamsaccharase for *Mycobacteria,* this latter marker being a negative selection marker.

[0024] Preferred bacterial vectors are listed hereafter as illustrative but not limitative examples: pQE70, pQE60, pQE-9 (Quiagen), pD10, phagescript, psiX174, p.Bluescript SK, pNH8A, pNH16A, pNH18A, pNH46A (Stratagene); pKK223-3, pKK233-3, pDR540, pRIT5 (Pharmacia); pWLNEO, pSV2CAT, pOG44, pXT1, pSG (Stratagene); pSVK3, pBPV, pMSG, pSVL (Pharmacia); pQE-30 (QIA express).

[0025] Preferred bacteriophage recombinant vectors of the invention are P1 bacteriophage vectors such as described by Sternberg N.L. (1992;1994).

[0026] A suitable vector for the expression of any of the pain associated polypeptides used in the invention or fragments thereof, is a baculovirus vector that can be propagated in insect cells and in insect cell-lines. A specific suitable host vector system is the pVL 1392/1393 *baculovirus* transfer vector (Pharmingen) that is used to transfect the SF9 cell line (ATCC N°CRL 1711) that is derived from *Spodoptera frugiperda.*

[0027] The recombinant expression vectors of in the invention may also be derived from an adenovirus. Suitable adenoviruses are described by Feldman and Steig (1996) or Ohno *et al.* (1994). Another preferred recombinant adenovirus is the human adenovirus type two or five (Ad 2 or Ad 5) or an adenovirus of animal origin (Patent Application WO 94/26914)

[0028] Particularly preferred retrovirus for the preparation or construction of retroviral *in vitro* or *in vivo* gene delivery vehicles include retroviruses selected from the group consisting of Mink-Cell Focus Inducing Virus, Murine Sarcoma Virus, and Ross Sarcoma Virus. Other preferred retroviral vectors are those described in Roth *et al.* (1996), in PCT Application WO 93/25234, in PCT Application WO 94/06920, and also in Roux *et al.* (1989), Julan *et al.*(1992) and Nada *et al.* (1991).

[0029] Yet, another viral vector system that is contemplated is the Adeno Associated Viruses (AAV) such as those described by Flotte *et al.* (1992), Samulski *et al.* (1989) and McLaughlin *et al.* (1996).

Host cells expressing pain associated polypeptides

[0030] Host cells that endogenously express pain associated polypeptides or have been transformed or transfected with one of the nucleic acid ssequences described herein, or with one of the recombinant vector described above, particularly a recombinant expression vector, can be used in the present invention. Also included are host cells that are transformed (prokaryotic cells) or are transfected (eukaryotic cells) with a recombinant vector such as one of those described above.

[0031] Preferred host cells used as recipients for the expression vectors used in the invention are the following:

(a) prokaryotic host cells: *Escherichia coli,* strains. (i.e. DH5-α, strain) *Bacillus subtilis, Salmonella typhimurium* and strains from species like *Pseudomonas, Streptomyces* and *Staphylococcus* for the expression of up and down-regulated nucleic acid sequence modulated by pain, characterized by having at least 80% sequence identity with any of the nucleic acid sequences of Tables I - VI. Plasmid propagation in these host cells can provide plasmids for transfecting other cells.

(b) eukaryotic host cells: HeLa cells (ATCC N°CCL2; N°CCL2.1; N°CCL2.2), Cv 1 cells (ATCC N°CCL70), COS cells (ATCC N°CRL 1650; N°CRL 1651), Sf-9 cells (ATCC N°CRL 1711), C127 cells (ATCC N°CRL-1804), 3T3 cells (ATCC N°CRL-6361), CHO cells (ATCC N°CCL-61), human kidney 293 cells (ATCC N° 45504; N°CRL-1573), BHK (ECACC N°84100 501; N°84111301), PC12 (ATCC N° CRL-1721), NT2, SHSYSY (ATCC N° CRL-2266), NG108 (ECACC N°88112302) and F11, SK-N-SH (ATCC N° CRL-HTB-11), SK-N-BE(2) (ATCC N° CRL-2271), IMR-32 (ATCC N° CCL-127). A preferred system to which the nucleic acids of the invention can be expressed are

neuronal cell lines such as PC12, NT2, SHSY5Y, NG108 and F11, SK-N-SH, SK-N-BE(2) , IMR-32 cell lines, COS cells, 3T3 cells, HeLa cells, 292 cells and CHO cells. The above cell lines could be used for the expression of any of the nucleic acid sequences of Tables I - VI.

[0032] When a nucleic acid sequence of any of Tables I - X is expressed using a neuronal cell line, the sequence can be expressed through an endogenous promoter or native neuronal promoter, or an exogenous promoter. Suitable exogenous promoters include SV40 and CMV and eukaryotic promoters such as the tetracycline promoter. The preferred promoter when pain associated molecules are endogenously expressed is an endogenous promoter. A preferred promoter in a recombinant cell line is the CMV promoter.

[0033] In a specific embodiment of the host cells described above, these host cells have also been transfected or transformed with a polynucleotide or a recombinant vector for the expression of a natural ligand of any of the nucleic acid sequences of any of Tables I - VI or a modulator of these expression products.

PROTEINS, POLYPEPTIDES AND FRAGMENTS

[0034] The expression products of the nucleic acid sequences of Tables I - VI or fragment(s) thereof can be prepared using recombinant technology, from cell lines or by chemical synthesis. Recombinant methods, chemical methods or chemical synthetic methods can be used to modify a gene in order to introduce into the gene product, or a fragment of the gene product, features such as recognition tags, cleavage sites or other modifications. For efficient polypeptide production, the endogenous expression system or recombinant expression system should allow the expression products to be expressed in a manner that will allow the production of a functional protein or fragment thereof which can be purified. Preferred cell lines are those that allow high levels of expression of polypeptide or fragments thereof. Such cell lines include cell lines which naturally express the nucleic acid sequence of Tables I - VI or common mammalian cell lines such as CHO cells or COS cells, etc, or more specific neuronal cell lines such as PC12. However, other cell types that are commonly used for recombinant protein production such as insect cells, amphibian cells such as oocytes, yeast and prokaryotic cell lines such as *E. coli* can also be used.

[0035] The expression products of Tables I - VI or fragments thereof can be utilized in screens to identify potential therapeutic ligands, either as a purified protein, as a protein chimera such as those produced in phage display, as a cell membrane (lipid or detergent) preparation, or in intact cells.

[0036] The invention also relates generally to the use of proteins, peptides and peptide fragments for the development of screening technologies for the identification of molecules for the prevention or treatment of pain, and the development of diagnostic tools for the identification and characterization of pain. These peptides include expression products of the nucleic acid sequences of Tables I - VI and purified or isolated polypeptides or fragments thereof having at least 90%, preferably 95%, more preferably 98% and most preferably 99% sequence identity with the any of the expression products of nucleic acid sequences of Tables I - VI. Expressed peptides and fragments of any of these nucleic acid sequences can be used to develop screening technologies for the identification of novel molecules for the prevention or treatment of pain. These screening technologies could also be used to ascribe new pain therapeutic indications to molecules, which have not previously been ascribed for the prevention or treatment of pain. Furthermore the said expressed peptides and fragments can be used as diagnostic tools and for the development of diagnostic tools.

SCREENING METHODS

[0037] As discussed above, we have identified nucleic acid sequences whose expression is regulated by pain, particularly chronic pain and more particularly diabetic pain. The expression products of these nucleic acids can be used for screening ligand molecules for their ability to prevent or treat pain, and particularly, but not exclusively, chronic pain. The main types of screens that can be used are described below. The test compound can be a peptide, protein or chemical entity, either alone or in combination(s), or in a mixture with any substance. The test compound may even represent a library of compounds.

[0038] The expression products of any of the nucleic acid sequences of Tables I - VI or fragments thereof can be utilized in a ligand binding screen format, a functional screen format or invivo format. Examples of screening formats are provided.

A) Ligand binding screen

[0039] In ligand binding screening a test compound with is contacted with an expression product of one of the sequences of Tables I - VI, and the ability of said test compound to interact with said expression product is determined, e.g. the ability of the test compound(s) to bind to the expression product is determined. The expression product can be a part of an intact cell, lipidic preparation or a purified polypeptide(s), optionally attached to a support, such as

beads, a column or a plate etc.

[0040] Binding of the test compound is preferably performed in the presence of a ligand to allow an assessment of the binding activity of each test compound. The ligand may be contacted with the expression product either before, simultaneously or after the test compound. The ligand should be detectable and/or quantifiable. To achieve this, the ligand can be labelled in a number of ways, for example with a chromophore, radioactive, fluorescent, phosphorescent, enzymatic or antibody label. Methods of labelling are known to those in the art. If the ligand is not directly detectable it should be amenable to detection and quantification by secondary detection, which may employ the above technologies. Alternatively the expression product or fragment thereof can be detectable or quantifiable. This can be achieved in a similar manner to that described above.

[0041] Binding of the test compound modifies the interaction of the ligand with its binding site and changes the affinity or binding of the ligand for/to its binding site. The difference between the observed amount of ligand bound relative to the theoretical maximum amount of ligand bound (or to the ligand bound in the absence of a test compound under the same conditions) is a reflection of the binding ability (and optionally the amount and/or affinity) of a test compound to bind the expression product.

[0042] Alternatively, the amount of test compound bound to the expression product can be determined by a combination of chromatography and spectroscopy. This can be achieved with technologies such as Biacore (Amersham Pharmacia). The amount of test compound bound to the expression product can also be determined by direct measurement of the change in mass upon compound or ligand binding to the expression product. Alternatively, the expression product, compound or ligand can be fluorescently labelled and the association of expression product with the test compound can be followed by changes in Fluorescence Energy Transfer (FRET).

[0043] The invention therefore includes a method of screening for pain alleviating compounds, comprising:

a) contacting a test compound or test compounds in the presence of a ligand with an expression product of any of the nucleic acid sequences of Tables I - VI or with a cell expressing at least one copy of the expression product or with a lipidic matrix containing at least one copy of the expression product;
b) determining the binding of the test compound to the expression product, and
c) selecting test compounds on the basis of their binding abilities.

[0044] In the above method, the ligand may be added prior to, simultaneously with or after contact of the test compound with the expression product. Non limiting examples and methodology can be gained from the teachings of the *Molecular Probes handbook* and references therein (Molecular Probes, Inc., 4849 Pitchford Ave, Eugene, USA), *Methods in neurotransmitter receptor analysis* (Yamamura HI., Enna, SJ., and Kuhar, MJ., Raven Press New York, the *Glaxo Pocket Guide to Pharmacology*, Dr. Michael Sheehan, Glaxo Group Research Ltd, Ware, Herts SG12 0DP), *Bylund DB and Murrin LC* (2000, Life Sciences, 67 (24) 2897-911), *Owicki JC (2000, J. biomol Screen (5) 297-306), Alberts et al (1994, Molecular Biology of the Cell, 3rd Edn, Garland Publication Inc), Butler JE, (2000 Methods 22(1):4-23, Sanberg SA* (2000, Curr Opin Biotechnol 11(1) 47-53), and *Christopoulos A* (1999, biochem Pharmacol 58(5) 735-48).

B) Functional screening

(a) Kinase assays

[0045] The expression product of any of the nucleic acid sequences of Tables I - VI which encode a kinase, and in particular the nucleic acid sequence listed in Table I, is amenable to screening using kinase assay technology.

[0046] Kinases have the ability to add phosphate molecules to specific residues in ligands such as binding peptides in the presence of a substrate such as adenosine triphosphate (ATP). Formation of a complex between the kinase, the ligand and substrate results in the transfer of a phosphate group from the substrate to the ligand. Compounds that modulate the activity of the kinase can be determined with a kinase functional screen. Functional screening for modulators of kinase activity therefore involves contacting one or more a test compounds with an expression product of one of the nucleic acid sequences of Tables I - VI which encodes a kinase, and determining the ability of said test compound to modulate the transfer of a phosphate group from the substrate to the ligand.

[0047] The expression product can be part of an intact cell or of a lipidic preparation or it can be a purified polypeptide (s), optionally attached to a support, for example beads, a column, or a plate. Binding is preferably performed in the presence of ligand and substrate to allow an assessment of the binding activity of each test compound.

[0048] The ligand should contain a specific kinase recognition sequence and it should not be phosphorylated at its phosphoryation site. The ligand and/or substrate may be contacted with the kinase either before, simultaneously or after the test compound. Optionally the substrate may be labelled with a kinase transferable labelled phosphate. The assay being monitored by the phosphorylation state of the substrate and/or the ligand. The ligand should be such that its phosphorylation state can be determined. An alternative method to do this is to label the ligand with a phosphor-

ylation-state-sensitive molecule. To achieve this, the ligand can be labelled in a number of ways, for example with a chromophore, radioactive, fluorescent, phosphorescent, enzymatic or antibody label. If the ligand is not directly detectable it should be amenable to detection and quantification by secondary detection, which may employ the above technologies. Such technologies are known to those in the art.

[0049] Binding of the test compound to the kinase modifies its ability to transfer a phosphate group from the substrate to the ligand. The difference between the observed amount of phosphate transfer relative to the theoretical maximum amount of phosphate transfer is a reflection of the modulatory effect of the test compound. Alternatively, the degree of phosphate transfer can be determined by a combination of chromatography and spectroscopy. The extent of phosphorylation of the ligand peptide or dephosphorylation of the substrate can also be determined by direct measurement. This can be achieved with technologies such as Biacore (Amersham Pharmacia).

[0050] The invention also provides a method for screening compounds for the ability to relieve pain, which comprises:

(a) contacting one or more test compounds in the presence of ligand and substrate with an expression product of any of the sequences of Tables I - VI which is a kinase or with a cell containing at least 1 copy of the expression product or with a lipidic matrix containing at least 1 copy of an expression product;
(b) determining the amount of phosphate transfer from the substrate to the ligand; and
(c) selecting test compounds on the basis of their capacity to modulate phosphate transfer.

[0051] Optionally ligand, substrate and/or other essential molecules may be added prior to contacting the test compound with expression product of step (a) or after step (a). Non limiting examples and methodology can be gained from the teachings of the *Molecular Probes handbook* and references therein (Molecular Probes, Inc., 4849 Pitchford Ave, Eugene, USA), *Methods in Molecular Biology 2000*; 99: 191-201, *Oncogene* 2000 20; 19(49): 5690-701, and *FASAB Journal,* (10, 6, P55, P1458, 1996, Pocius D Amrein K *et al*).

b) Receptor assays

[0052] An expression product of any of the nucleic acid sequences of Tables I - VI which encodes a receptor, and in particular any of the nucleic acid sequences listed in Table II, is amenable to screening using receptor assay technology.

[0053] Receptors are membrane associated proteins that initiate intracellular signalling upon ligand binding. Therefore, the identification of molecules for the prevention and treatment of pain can be achieved with the use of a ligand binding assay, as outlined above. Such an assay would utilize an endogenous or non-endogenous ligand as a component of the ligand binding assay. The binding of this ligand to the receptor in the presence of one or more test compounds would be measured as described above. Such is the nature of receptors that the assay is usually, but not exclusively performed with a receptor as an intact cell or membraneous preparation.

[0054] The invention therefore includes a method of screening for pain alleviating compounds, comprising:

a) contacting a test compound or test compounds in the presence of a ligand with a cell expressing at least one copy of the expression product of any of the sequences of Tables I - VI which is a receptor or with a lipidic matrix containing at least one copy of the expression product;
b) determining the binding of the test compound to the expression product, and
c) selecting test compounds on the basis of their binding abilities.

c) Transporter protein assays

[0055] An expression product of any of the nucleic acid sequences of Tables I - VI which encodes a transporter protein, and in particular any of the nucleic acid sequences listed in Table III, is amenable to screening using transporter protein assay technology. Non limiting examples of technologies and methodologies are given by *Carroll FI, et al* (1995, Medical Research Review, Sep15 (5) p419-444), *Veldhuis JD and Johnson MI* (1994, Neurosci. Biobehav Rep., winter 18(4) 605-12), *Hediger MA and Nussberger S* (1995, Expt Nephrol. July-Aug 3(4) p211-218, *Endou H and Kanai Y,* (1999, Nippon Yakurigaku Zasshi, Oct. 114 Suppl 1:1p-16p), *Olivier B et al* (2000, Prog. Drug Res., 54, 59-119), *Braun A et al* (2000, Eur J Pharm Sci, oct 11, Suppl 2 S51-60) and *Molecular Probes handbook and references therein* (Molecular Probes, Inc., 4849 Pitchford Ave, Eugene, USA).

[0056] The main function of transporter proteins is to facilitate the movement of molecules across a cellular membrane. Compounds that modulate the activity of transporter proteins can be determined with a transporter protein functional screen. Functional screening for modulators of transporter proteins comprises contacting at least one test compound with an expression product as aforesaid which is a transporter protein and determining the ability of said test compound to modulate the activity of said transporter protein. The expression product can be part of an intact cell,

or lipidic preparation, optionally attached to a support, for example beads, a column or a plate. Binding is preferably performed in the presence of the molecule to be transported, which should only able to pass through a cell membrane or lipidic matrix with the aid of the transporter protein. The molecule to be transported should be able to be followed when it moves into a cell or through a lipidic matrix. Preferably the molecule to be transported is labelled to aid in characterization, e.g. with a chromophore, radioactive, fluorescent, phosphorescent, enzymatic or antibody label. If the molecule to be transported is not directly detectable it should be amenable to detection and quantification by secondary detection, which may employ the above technologies. The molecule to be transported may be contacted with the transporter protein before, simultaneously with or after the test compound. If binding of the test compound to the transporter protein modifies its ability to transport molecules through a membraneous or lipidic matrix, then the difference between the observed amount of transported molecule in a cell/or through a lipidic matrix relative to the theoretical maximum amount is a reflection of the modulatory effect of the test compound.

[0057] The invention further provides a method for screening compounds for their ability to relieve pain, comprising

a) contacting at least one test compound in the presence of transporter molecules with a cell containing at least one copy of an expression product of any of the sequences of Tables I - VI which is a transporter protein or with a lipidic matrix containing at least one copy of the expression product;
c) measuring the movement of transported molecules into or from the cell, or across the lipidic matrix; and
d) selecting test compounds on the basis of their ability to modulate the movement of transported molecules.

d) G-protein coupled receptor protein assays

[0058] An expression product of any of the nucleic acid sequences of Tables I - VI that encodes a G-protein coupled receptor protein, and in particular any of the nucleic acid sequences listed in Table IV, is amenable to screening using G-protein coupled receptor protein assay technology.

[0059] G-protein coupled receptor proteins (GPCRs) are membrane associated proteins whose main function is to transduce a signal through a cellular membrane. Upon ligand binding, GPCRs undergo a conformational change that allows complexing of the GPCRs with a G-protein. G-proteins possess a GTP/GDP binding site. The formation of the G-protein/ligand complex allows exchange of GTP for GDP, resulting in a conformational change of the G-protein. This conformational change initiates signal transduction.

[0060] Functional screening for modulators of GPCRs comprises contacting at least one test compound with an expression product as aforesaid which is a G-protein coupled receptor protein, and assessing the ability of the test compound(s) to modulate the exchange of GTP for GDP or the modulation of the GPCR signal transduction pathway. The expression product can be part of an intact cell or lipidic preparation, optionally attached to a support, for example beads, a column or a plate. Binding is preferably performed in the presence of a ligand, G-protein and GTP/GDP to allow an assessment of the binding activity of each test compound. Alternatively components of the signaling pathway are also included. In particular, in a preferred embodiment, a labeled GTP is used and the ability of the test compound (s) to modulate the exchange of GTP to GDP is determined. A further optional characteristic of the assay can be the inclusion of a reporter molecule that enables monitoring the regulation of the signaling pathway. The ligand may be contacted with the GPCR before, simultaneously with, or after the test compound. Binding of the test compound to the GPCR modifies its ability to modulate the exchange of GTP for GDP and hence the modulation of signal transduction. The difference between the observed amount of GTP exchanged for GDP relative to the theoretical maximum amount of GTP is a reflection of the modulatory effect of the test compound. Likewise the relative activities of signal transduction reporter molecules are also a reflection of the modulatory effect of the test compound. Non limiting examples of technologies and methodologies can be found in *Molecular Probes handbook* and references therein (Molecular Probes, Inc., 4849 Pitchford Ave, Eugene, USA), *Glaxo Pocket Guide to Pharmacology,* (Michael Sheehan, Pharmacology Division staff, Glaxo Group Research Ltd., Ware, Herts SC12 0DP) and *Xing et al* (2000, J. Recept. Signal. Transduct. Res. 20(40 189-210).

[0061] The invention provides a method of screening compounds for their ability to relieve pain, comprising:

a) contacting at least one test compound in the presence of a ligand, GTP/GDP, G-protein with a cell containing at least one copy of an expression product of a sequence of Tables I - VI as aforesaid which is a G-protein coupled receptor protein or with a lipidic matrix containing at least one copy of the expression product;
b) measuring the exchange of GTP for GDP, and
c) selecting test compounds on the basis of their ability to modulate said exchange.

In the above method, the ligand, GTP/GDP, G-protein and other essential molecules can be added before, simultaneously with or after the contacting of the test compound(s) with the cell line or lipidic matrix in step (a).

e) DNA-binding protein assays

[0062] An expression product of any of the nucleic acid sequences of Tables I - VI that encodes a DNA-binding protein, and in particular any of the nucleic acid sequences listed in Table V, is amenable to screening using DNA-binding protein assay technology.

[0063] DNA binding proteins are proteins that are able to complex with DNA. The complexing of the DNA binding protein with the DNA in some instances requires a specific nucleic acid sequence. Screens can be developed in a similar manner to ligand binding screens as previously indicated and will utilise DNA as the ligand. DNA-binding protein assays can be carried using similar principles described in ligand binding assays as described above. Non limiting examples of methodology and technology can be found in the teachings of *Haukanes BI and Kvam* C (Biotechnology, 1993 Jan 11 60-63), *Alberts B et al* (Molecular Biology of the Cell, 1994, 3rd Edn., Garland Publications Inc, *Kirigiti P and Machida CA* (2000 Methods Mol Biol, 126, 431-51) and *Molecular Probes handbook* and references therein (Molecular Probes, Inc., 4849 Pitchford Ave., Eugene, USA).

[0064] The invention therefore includes a method of screening for pain alleviating compounds, comprising:

a) contacting a test compound or test compounds in the presence of a plurality of nucleic acid sequences with an expression product of any of the nucleic acid sequences of Tables I - VI which is a DNA binding protein or with cells expressing at least one copy of the expression product or with a lipidic matrix containing at least one copy of the expression product;
b) determining the binding of the test compound to the expression product, and
c) selecting test compounds on the basis of their binding abilities.
In the above method, the plurality of nucleic acid sequence may be added prior to, simultaneously with or after contact of the test compound with the expression product.

f) Assays using other enzymes

[0065] Expression products of any of the nucleic acid sequences of Tables I - VI that encode other enzymes, e.g. ligases, lyases, oxidoreductases, transferases and hydrolases, and in particular any of the nucleic acid sequences listed in Table VI, is amenable to screening using appropriate assay technology.

[0066] Each class of enzyme has a defined function. Ligases have the property of being able to splice molecules together. This is achieved with the conversion of ATP substrate to AMP. Therefore, the activity of a ligase can be followed by monitoring the conversion of ATP to AMP. Such technologies are known to those in the art. Non limiting examples and methodologies are illustrated by *Ghee. T. Tan et al* (1996,Biochem J. 314, 993-1000, *Yang SW et al* (1992, 15: 89(6) 2227-31 and refrences therein, and in *Molecular Probes handbook* and references therein (Molecular Probes, Inc., 4849 Pitchford Ave, Eugene, USA).

[0067] The invention also provides a methods of screening for pain alleviating compounds, comprising;

a) contacting one or more test compounds in the presence of ATP with an expression product of any of the sequences of Tables I - VI which is a ligase or with a cell expressing at least 1 copy of a expression product or with a lipidic matrix containing at least 1 copy of an expression product which is a ligase;
b) determining the amount of ATP converted to AMP, and
c) selecting test compounds on the basis of their ability to modulate said conversion.

[0068] Lyases are enzymes which catalyse the cleavage of by reactions other than hydrolysis. These enzymes can be grouped into seven groups according to type of bond cleaved. These groups are carbon-carbon lyases (E.C. No 4.1), carbon-oxygene lyases (E.C. No 4.2), carbon-nitrogen lyases (E.C. No 4.3), carbon-sulphur lyase (E.C. No 4.4) carbon-halide lyases (E.C. No 4.5), phosphorous-oxygene lyases (E.C. No 4.6) and other lyases (E.C. No 4.99) (Analytical Biochemistry 3rd Edn, David J. Holme and Hazel Peck, Longman press). The enzyme commission number (E. C.) of the International Union of Biochemistry relates to the type of reaction catalysed by the enzyme. Further *teachings on how to develop assays and screens for lyases can be obtained from Methods in Enzymology* (Academic Press).

[0069] Oxidoreductases are enzymes that catalyse the transfer of hydrogen or oxygen atoms or electrons. These enzymes can by sub-grouped into twenty categories according to their specific mode of action. These groups are oxidoreductases acting on the CH-OH group of donors (E.C. Nol.1 oxidoreductases acting on the aldehyde or oxo group of donors (E.C. No 1.2), oxidoreductases acting on the CH-CH group of the donor (E.C. No 1.3), oxidoreductases acting on the CH-NH2 group of donors (E.C. 1.4), oxidoreductases acting on the CH-NH group of donor (E.C. 1.5), oxidoreductases acting on the NADH or NADPH (E.C. No 1.6), oxidoreductases acting on other nitrogen compounds as donors (E.C. No 1.7), oxidoreductases acting on a sulphur group of donors (E.C. No 1.8), oxidoreductases acting on a haem group of donors (E.C. No1.9), oxidoreductases acting on diphenols and related substances as donors (E.

C. 1.10), oxidoreductases acting on hydrogen peroxide as acceptor (E.C. No 1.11), oxidoreductases acting on hydrogen as donor (E.C. No 1.12), oxidoreductases acting on single doners with incorporation of molecular oxygen (E.C. No 1.13), oxidoreductases acting on paired donors with incorporation of molecular oxygen (E.C. No 1.14), oxidoreductases acting on superoxide radicals as acceptors (E.C. 1.15), oxidoreductases oxidizing metal ions (E.C. No 1.16), oxidoreductases acting on -CH2 groups (E.C. No 1.17), oxidoreductases acting on reduced ferredoxin as donor (E.C. No 1.18), oxidoreductases acting on reduced flavodoxin as donor (E.C. No 1.19) and other oxidoreductases (E.C. No 1.97) (Analytical Biochemistry 3rd Edn, David J. Holme and Hazel Peck, Longman Press). The enzyme commission number (E.C.) of the International Union of Biochemistry relates to the type of reaction catalysed by the enzyme. Further teachings on how to develop assays and screens for oxidoreductases can be obtained from *Methods in Enzymology* (Academic Press) with special reference to volume 249.

[0070] Transferases are enzymes that catalyse the transfer of specific groups. They are classified into eight sub groups according to function, transferring one-carbon group (E.C. No 2.1), Transfering aldehyde or ketonic residues (E.C. No 2.2), Acetyltransferases (E.C. 2.3), glycosyltransferases (E.C. No 2.4), transferring alkyl or aryl groups other than methyl groups (E.C. No 2.5), transferring nitrogeneous groups (E.C. No 2.6), transferring phosphorous-containing groups (E.C. No 2.7) and transferring sulphur-containing groups (E.C. No 2.8) (Analytical Biochemistry 3rd Edn, David J. Holme and Hazel Peck, Longman Press). The enzyme commission number (E.C.) of the International Union of Biochemistry relates to the type of reaction catalysed by the enzyme. Further teachings on how to develop assays and screens for transferases can be obtained from Methods in Enzymology (Academic Press).

[0071] Hydrolases are enzymes that catalyse hydrolytic reactions and are sub-grouped into eleven classes according to the type of reaction they carry out. Hydrolases acting on ester bonds (E.C. No 3.1), hydrolases acting on glycosyl compounds (E.C. No 3.2), hydrolases acting on ether bonds (E.C. No 3.3), hydrolases acting on peptide bonds (E.C. No 3.4), hydrolases acting on carbon-nitrogen bonds, other than peptide bonds (E.C. No 3.5), hydrolases acting on acid anhydrides (E.C. No 3.6), hydrolases acting on acid anhydrides (E.C. No 3.6), hydrolases acting on carbon-carbon bonds (E.C. No 3.7), hydrolases acting on halide bonds (E.C. No 3.8), hydrolases acting on phosphorous-nitrogen bonds (E.C. No 3.9), hydrolases acting on sulphur-nitrogen bonds (E.C. No 3.10) and hydrolases acting on carbon-phosphorous bonds (Analytical Biochemistry 3rd Edn, David J. Holme and Hazel Peck, Longman Press). The enzyme commission number (E.C.) of the International Union of Biochemistry relates to the type of reaction catalysed by the enzyme. Further teachings on how to develop assays and screens for hydrolases can be obtained from Methods in Enzymology (Academic Press) with special reference to volume 249.

C) In vivo functional screen

[0072] Any of the nucleotide sequences described in Tables I - VI or homologues thereof may be inserted by means of an appropriate vector into the genome of a lower vertebrate or of an invertebrate animal or may be inactivated or down regulated in the genome of said animal. The resulting genetically modified animal may be used for screening compounds for effectiveness in the regulation of pain. The invertebrate may, for example, be a nematode e.g. *Caenorhabditis elegans,* which is a favourable organism for the study of response to noxious stimuli. Its genome sequence has been determined, see *Science,* **282,** 2012 (1998), it can be bred and handled with the speed of a microorganism (it is a self-fertilizing hermaphrodite) and can therefore be used in a high throughput screening format (WO 00/63424, WO 00/63425, WO 00/63426 and WO 00/63427), and it offers a full set of organ systems, including a simple nervous system and contains many similarly functioning genes and signaling pathways to mammals. A thermal avoidance model based on a reflexive withdrawal reaction to an acute heat stimulus has been described by Wittenburg *et al, Proc. Natl. Acad. Sci.USA,* **96,** 10477-10482 (1999), and allows the screening of compounds for the treatment of pain with the modulation of pain sensation as an endpoint.

[0073] The genome of *C. elegans* can be manipulated using homologous recombination technology which allows direct replacement of nucleic acids encoding *C. elegans* with their identified mammalian counterpart. Replacement of these nucleic acids with those nucleic acids outlined above would allow for the direct screening of test compound(s) with their expression products. Any of the pain-related genes described above may be ligated into a plasmid and introduced into oocytes of the worm by microinjection to produce germline transformants. Successful plasmid injection into *C. elegans* and expression of inserted sequences has been reported by Devgen B.V., Ghent, Belgium. It is also possible to produce by routine methods worms in which the target sequences are down-regulated or not expressed (knock-out worms). Further non limiting examples of methodology and technology can be found in the teachings of *Hazendonk et al* (1997, Nat genet. 17(1) 119-21), *Alberts et al,* (1994, Molecular Biology of the Cell 3rd Ed. Garland Publishing Inc, *Caenorhabditis elegans* is anatomically and genetically simple), *Broverman S et al,* (1993, PNAS USA 15;90(10) 4359-63) and Mello et al (1991, 10(12)3959-70).

[0074] A further method for screening compounds for ability to modify response to pain, e.g. relieve pain, comprises:

(a) contacting one or more test compounds with at least one *C elegans* containing at least one copy of a sequence

as set out above;
(b) subjecting the *C. elegans* to a nociceptive stimulus;
(c) observing the response of the *C. elegans* to said stimulus; and
d) selecting test compounds on the basis of their ability to modify the response of *C. elegans* to said stimulus.

DIAGNOSTIC TOOLS AND KITS

Affinity peptides, ligands and substrates

[0075] Pain associated polypeptides and fragments thereof can be detected at the tissue and cellular levels with the use of affinity peptides, ligands and substrates, which will enable a skilled person to define more precisely a patient's ailment and help in the prescription of a medicament. Such affinity peptides are characterized in that firstly they are able to bind specifically to a pain associated polypeptide, and secondly that they are capable of being detected. Such peptides can take the form of a peptide or polypeptide for example an antibody domain or fragment, or a peptide/polypeptide ligand or substrate, or a polypeptide complex such as an antibody.

[0076] The preparation of such peptides and polypeptides are known to those in the art. Antibodies, these may be polyclonal or monoclonal, and include antibodies derived from immunized animals or from hybridomas, or derivatives thereof such as humanized antibodies, Fab or F(ab')2 antibody fragments or any other antibody fragment retaining the antigen binding specificity.

[0077] Antibodies directed against pain-associated gene product molecules may be produced according to conventional techniques, including the immunization of a suitable mammal with the peptides or polypeptides or fragment thereof. Polyclonal antibodies can be obtained directly from the serum of immunized animals. Monoclonal antibodies are usually produced from hybridomas, resulting from a fusion between splenocytes of immunized animals and an immortalized cell line (such as a myeloma). Fragments of said antibodies can be produced by protease cleavage, according to known techniques. Single chain antibodies can be prepared according to the techniques described in US 4,946,778. Detection of these affinity peptides could be achieved by labeling. technologies which allow detection of peptides, such as enzymatic labeling, fluorescence labeling or radio-labeling are well known to those in the art. Optionally these affinity peptides, ligands and substrates could themselves be detected with the use of a molecule that has specific affinity to the peptides, ligands and substrates and is itself labeled.

[0078] The invention further provides a kit comprising;

(a) affinity peptide and/or ligand and/or substrate for an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain ; and

(b) a defined quantity of an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal both in response to first and second models of neuropathic or central sensitization pain,

for simultaneous, separate or sequential use in detecting and/or quantifying an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain.

Complimentary nucleic acids

[0079] Pain associated nucleic acid sequences can be characterized at the tissue and cellular levels with the use of complimentary nucleic acid sequences. Detection of the level of expression of pain associated nucleic acid sequences can help in the prognosis of a pain condition and the prescription of a medicament. These complimentary nucleic acids are characterized in that they can hybridize to a pain associated nucleic acid sequence and their presence can be detected through various techniques. Such techniques are known to those in the art and may include detection by polymerase chain reaction or detection by labeling of complimentary nucleic acid sequences by enzymatic labeling, affinity labeling fluorescent labeling or radio labeling. Complimentary strand nucleic acid sequences of this invention are 10 to 50 bases long, more preferably 15 to 50 bases long and most preferably 15 to 30 bases long, and hybridize to the coding sequence of the nucleic acid sequence.

[0080] A further aspect of this invention is a kit that comprises:

(a) nucleic acid sequences capable of hybridization to a nucleic acid sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain; and
(b) a defined quantity of one or more nucleic acid sequences capable of hybridization to a nucleic acid sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or

central sensitization pain, for simultaneous, separate or sequential use in detecting and/or quantifying a gene sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain.

IDENTIFICATION AND VALIDATION

[0081] Subtractive hybridization enables the identification of nucleic acid sequences whose expression profiles are modified by a stimulus. Upon stimulation of a system (in the case of this invention a nociceptive stimulus on an animal model) all observed changes in the level of nucleic acid sequence expression are due to the reaction of the system to the stimulus. Characterization of these changes in expression by way of identification of nucleic acid sequence and level of expression is both identification and validation.

[0082] The inventors have developed a four step process which allows for the simultaneous identification and validation of nucleic acid sequences whose expression are regulated by a pain stimulus, preferably a chronic pain stimulus, and more preferably a diabetic pain stimulus. This process may comprise the following steps:

(a) induction of a nociceptive stimulus in test animals;
(b) extraction of nucleic acids from specific neuronal tissue of test and control animals;
(c) selective amplification of differentially expressed nucleic acid sequences; and
(d) identification and characterization of differentially expressed gene products that are modulated by a nociceptive stimulus.

[0083] The above process is described in more detail below.

(a) Induction of nociceptive stimulus

[0084] The effect of the selected nociceptive stimulus on the test animal needs to be confirmable. The test subjects are therefore a species that has a "developed" nervous system, preferably similar to that of humans, most preferably rats or mice. Advantageously, the nociceptive stimulus is analogous to known pain paradigms in humans. One such paradigm of pain is the pain associated with diabetes, which can be induced in rodents with the use of streptozotocin (STZ). The present application requires the sequences to be down-regulated in two pain models which may be, but are not limited to models of neuropathic pain and/or central sensitization, and in which diabetic pain provides the first model and mechanical damage e.g. to a nerve leading into the spine can provide an appropriate second model.

[0085] Streptozotocin (STZ) induces hyperglycemia and Type 1 diabetes mellitus in rats. In particular, STZ contains a glucose analogue that allows it to be taken up by the glucose transporter 2 present on the surface of pancreatic β cells, the site of insulin synthesis. Once inside the cell, STZ causes a reduction in the level of nicotinamide adenine dinucleotide (NAD^+). The decrease in NAD^+ levels eventually leads to necrosis of the pancreatic β cell, causing a reduction in insulin levels and then diabetes, leading to neuropathy (diabetic) and neuropathic pain (R. B. Weiss, *Cancer Treat. Rep.*, **66**, 427-438 1982, Guy *et al, Diabetologica*, **28**, 131-137 1985; Ziegler *et al, Pain*, **34**, 1-10 1988; Archer *et al, J. Neural. Neurosurgeon. Psychiatry*, **46**, 491-499 1983). The diabetic rat model has been shown to be a reliable model of hyperalgesia. We have used an STZ-induced diabetic rat model to create a state of hyperlagesia that can be compared with control animals (Courteix *et al, Pain*, **53**, 81-88 1993).

[0086] Three models of neuropathic and/or central sensitization pain in rats, which involve nerve injury, may be used, see Ralston, DD (1998) Present models of neuropathic pain. *Pain Rev.* **5**: 83-100. The injuries are caused by (1) loosely tying four chromic gut sutures around the sciatic nerve (CCI model developed by Bennett,GJ and Y-K Xie, A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man, *Pain* **33**: 87-107 (1988), (2) tightly ligating one third to one half of the fibers in the sciatic nerve (model developed by Seltzer, Z, R Dubner, Y Shire, A novel behavioral model of neuropathic pain disorders produced in rats by partial sciatic nerve injury, *Pain* **43**: 205-218, 1990), and (3) tightly ligating the dorsal spinal nerve of a rat at the L5 or L5 and L6 levels (L5 model developed by Kim, SH and JM Chung, An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat, *Pain* **50**:355-363, 1992).

(b) Extraction of nucleic acids from neuronal tissue of test and control animals

[0087] The inventors have determined that RNA extraction of whole spinal cord nervous tissue would provide a way of identifying nucleic acid sequences whose expression in spinal tissue is modulated by streptozotocin induced diabetes or by a mechanical nerve damage model for neuropathic and/or central sensitization pain e.g. CCI. Test (subjected to the nociceptive stimulus) and control animals were sacrificed, and the tissue to be studied e.g. neural tissue separated. Techniques for so doing vary widely from animal to animal and will be familiar to skilled persons.

[0088] A cDNA library can be prepared from total RNA extracted from neural tissue of the test and control animals. Where possible, however, it is preferred to isolate the mRNA from the total RNA of the test and control animals, by affinity chromatography on oligo (dT)-cellulose, and then reverse transcribe the mRNA from the test and control animals to give test and control cDNA. Converting mRNA from the test and control animals to corresponding cDNA may be carried out by any suitable reverse transcription method, e.g. a method as described by Gubler & Hoffman, *Gene,* 25, 263-269 (1983). If desired a proprietary kit may be used e.g. the CapFinder PCR cDNA Library Construction Kit (Life Technologies) which is based on long-distance PCR and permits the construction of cDNA libraries from nanograms of total RNA.

(c) Selective amplification of differentially expressed nucleic acids

[0089] The reverse transcribed cDNA of the test and control animals is subjected to subtractive hybridisation and amplification so that differentially expressed sequences become selectively amplified and commonly expressed sequences become suppressed, so as to over-produce DNA associated with said nociceptic stimulus. A wide range of subtractive hybridisation methods can be used, but the preferred method is so-called suppression subtractive hybridisation, see US-A-5565340 and Diatchenko *et al, Proc. Nat. Acad. Sci. USA,* 93, 6025-6030 (1996), the disclosures of which are herein incorporated by reference. Kits for carrying out this method are available from CLONTECH Laboratories, Inc.

(d) Cloning and Sequencing the differentially expressed cDNA

[0090] The differentially expressed cDNA is ligated into a cloning vector, after which cells of *E. coli* are transformed with the vector and cultured. Positive clones are selected and lysed to release plasmids containing the cDNA insert. The plasmids are primed using forward and reverse primers to either side of the cloning site and the cDNA insert is sequenced. Vector and adaptor sequences are then removed from the output data from the sequencer, leaving only the nucleotide sequence of the differentially expressed gene. The sequence is then checked against data held in a database for homology to known nucleotide sequences and genes, including expressed sequence tags (ESTs) and coding sequences for proteins.

(e) Validation of the above method

[0091] The importance of the sequences that we have identified in pain is confirmed by the fact that genes have been identified using this method that represent nucleic acid sequences which have previously been implicated in pain, including Calmodulin (pRCM1, Genebank X13933), Enkephalin (Genebank Y07503) and Neurotensin receptor type 2 (Genebank X97121).

[0092] The inventors have identified nucleic acid sequences of the MAP kinase pathway, a previously non pain-associated biological pathway. The inventors have subsequently shown that intra-spinal injection of a MEK inhibitor (MEK is part of the MAP kinase pathway) produces a powerful inhibition of pain (Patent application No US 60/144292). Subsequently, it has been shown that the MAP kinase is also implicated in acute inflammatory pain (Woolf *et al,* Nature Neuroscience 1999).

[0093] The invention will now be further described in the following Example.

EXAMPLE

Induction of diabetes

[0094] Diabetes was induced in adult (150-200g) male Sprague-Dawley rats (n=6) as described by Courteix *et al (supra).* Animals were injected intraperitoneally with streptozotocin (STZ)(50 mg/kg) dissolved in distilled water. Control or sham animals (age-matched animals, n=6) were injected with distilled water only.

Chronic Constrictive Injury (CCI)

[0095] Rats were anaesthetized with i.p. sodium phenobarbital, after which the common left sciatic nerve was exposed at the level of the middle of the thigh by blunt dissection through the biceps femoris and proximal to the sciatic trifurcation. Four ligatures (4.0 braided silk) were tied loosely around it with about 1mm spacing. The muscle was closed in layers and two wound clips were applied to close the skin incision. The wound was then covered with topical antibiotics.

Nociceptive testing

[0096] Static allodynia (a form of hyperlagesia) was measured using a method described by Chaplan *let al,* "Quantitative assessment of tactile allodinya in the rat paw", *J. Neurosci. Methods,* **53,** 55-63 (1994). A series of von Frey filaments of different buckling weight (i.e. the load required for the filament to bend) were applied to the plantar surface of the right hand paw. The starting filament had a buckling weight of 20g. Lifting of the paw was taken to be a positive result, in which case a filament with the next lowest buckling weight was used for the next measurement. The test was continued until a filament was found for which there was an absence of response for longer than 5 seconds whereas a re-test with the next heaviest filament gave a positive response. Animals were considered hyperalgesic if their thresholds were found to be <4g of those of comparable untreated rats, see Calcutt & Chaplan, "Spinal pharmacology of tactile allodynia in diabetic rats", *British J. Pharmacol,* **122,** 1478-1482 (1997).

Tissue Extraction

[0097] STZ-treated, CCI-treated and control animals were anaesthetized with 4% halothane and perfused with ice-cold 0.9% saline containing 1% citric acid (pH adjusted to 7.4 with NaOH). The animals were decapitated and the lumbar spinal cord exposed. A 2-centimetre length of spinal cord ending at L6 (lumbar-6 forward) was removed from the spinal column. Attached dorsal root ganglia and contaminating spinal connective tissues were removed. The spinal cord tissue was snap frozen in dry ice and isopentane. In the experiments that follow, procedures on the streptozocin-treated and control groups of animals are disclosed. It will be understood that for identification of CCI-treated animals the same experiments are performed, but using tissues from the CCI-treated animals and from control animals.

Total RNA Extraction

[0098] Total RNA was extracted from the pooled male rat tissues of the streptozocin-treated and control groups using the TRIZOL Reagent Kit (Life Technologies). Briefly, tissue samples were homogenised fully using a Polytron homogenizer in 1ml of TRIZOL reagent per 50-100mg of tissue. Homogenized samples were then incubated at room temperature for 5 minutes and phase separated using 0.2ml chloroform per 1ml TRIZOL reagent followed by centrifugation at 3,000g. The aqueous phase was transferred to a fresh tube and the RNA precipitated with an equal volume of isopropyl alcohol and followed by centrifugation at 10,000g. The RNA pellet was washed in 75% ethanol and re-centrifuged. The pellet was then air dried and re-suspended in water.

mRNA Extraction

[0099] In contrast to ribosomal RNA and transfer RNA, the vast majority of mRNAs of mammalian cells carry tracts of poly(A^+) at their 3' termini. mRNAs can therefore be separated from the bulk of cellular RNA by affinity chromatography on oligo (dT)-cellulose. mRNA was extracted from Total RNA using the MESSAGEMAKER Kit (Life Technologies) in which mRNA (previously heated to 65°C in order to disrupt secondary structures and so expose the poly (A^+) tails) was bound to oligo(dT) cellulose under high salt concentrations (0.5M NaCl) in a filter syringe. Unbound RNA was then washed away and the poly(A^+) mRNA eluted in distilled water. A tenth of the volume of 7.5 M Ammonium Acetate, 50μg of glycogen/ml mRNA sample and 2 volumes of absolute alcohol were then added to the samples which were placed at -20°C overnight. Following precipitation, the mRNA was spun down at 12,000g for 30 minutes at 4°C. RNAase free water was used to re-suspend the pellets, which were then and stored at -80°C.

PCR SELECT

[0100] The technique used was based on that of the CLONTECH PCR Select Subtraction Kit. The following protocol was performed using STZ-treated lumbar spinal cord Poly A + RNA as the 'Tester' and Sham lumbar spinal cord poly A^+ RNA as the 'Driver' (Forward Subtraction). A second subtraction experiment using the Sham lumbar spinal cord mRNA as the 'Tester' and STZ treated lumbar spinal cord mRNA as the 'Driver' (Reverse Subtraction) was performed in parallel using the same reagents and protocol. As a control for both experiments, the subtraction was also carried out using human skeletal muscle mRNA that had been provided by the manufacturer.

First-Strand cDNA Synthesis

[0101] 2 μg of PolyA^+ RNA and 1 μl of cDNA synthesis primer (10 μM) were combined in a 0.5ml Eppendorf tube and sterile H_2O was added where necessary to achieve a final volume of 5 μl. The contents were mixed gently and incubated in a thermal cycler at 70°C for 2 min. The tubes were then cooled on ice for two minutes, after which 2 μl of

5X First-strand buffer, 1 µl of dNTP mix (10 mM each), sterile H_2O and 1 µl of AMV reverse transcriptase (20 units/µl) was also added. The tubes were then placed at 42°C for 1.5 hr in an air incubator. First-strand cDNA synthesis was terminated by placing the tubes on ice. (the human skeletal muscle cDNA produced by this step was used as the 'control driver' in later steps).

Second-Strand cDNA Synthesis

[0102] 48.4 µl of Sterile H_2O, 16.0 µl of 5X Second-strand buffer, 1.6 µl of dNTP mix (10 mM) and 4.0 µl of 20X Second-strand enzyme cocktail were added to each of the first-strand synthesis reaction tubes. The contents were then mixed and incubated at 16°C in a thermal cycler for 2 hr. 6 units (2 µl) of T4 DNA polymerase was then introduced and the tubes were incubated for a further 30 min at 16°C. In order to terminate second-strand synthesis, 4 µl of 20X EDTA/glycogen mix was added. A phenol:chloroform extraction was then carried out using the following protocol:-

[0103] 100 µl of phenol:chloroform:isoamyl alcohol (25:24:1) was added to the tubes which were then vortexed thoroughly and centrifuged at 14,000 rpm for 10 min at room temperature. The top aqueous layer was removed and placed in a fresh tube. 100 µl of chloroform:isoamyl alcohol (24:1) was then added to the aqueous layer and the tubes were again vortexed and centrifuged at 14,000 rpm for 10 min. 40 µl of 4 M NH_4OAc and 300 µl of 95% ethanol were then added and the tubes centrifuged at 14,000 rpm for 20 min. The supernatant was removed carefully, then 500 µl of 80% ethanol was added to the pellet. The tubes were centrifuged at 14,000 rpm for 10 min and the supernatant was removed so that the pellet could be air-dried. The precipitate was then dissolved in 50 µl of H_2O. 6 µl was transferred to a fresh microcentrifuge tube. The remainder of the sample was stored at -20°C until needed.

***Rsa* I Digestion**

[0104] All products of the above procedures were subjected to a restriction digest, using the restriction endonuclease *Rsa* I, in order to generate ds cDNA fragments that are short and thus are optimal for subtraction hybridisation due to the standard kinetics of the hybridisation. Also, as *Rsa* I makes a double stranded cut in the middle of a recognition sequence, 'blunt ends' of a known nucleotide sequence are produced allowing ligation of adaptors onto these ends in a later step. The following reagents were added to the 6 µl product of the second hybridisation (see above): 43.5 µl of ds cDNA, 5.0 µl 10X *Rsa* I restriction buffer and 1.5 µl of *Rsa* I (10 units/ µl). The reaction mixture was incubated at 37°C for 1.5 hr. 2.5 µl of 20X EDTA/glycogen mix was used to terminate the reaction. A phenol:chloroform extraction was then performed as above (second-strand cDNA synthesis section). The pellet produced was then dissolved in 5.5 µl of H_2O and stored at -20°C until needed. The preparation of the experimental 'Driver' cDNAs and the control skeletal muscle cDNA was thus completed.

Adaptor Ligation

[0105] The adaptors were not ligated to the driver cDNA.

[0106] 1 µl of each *Rsa* I-digested experimental cDNA (from the *Rsa* I Digestion above) was diluted with 5 µl of sterile water. Preparation of the control skeletal muscle tester cDNA was then undertaken by briefly centrifuging the tube containing control DNA (*Hae* III-digest of ϕX174 DNA [3 ng/ µl]) and diluting 2 µl of the DNA with 38 µl of sterile water (to 150 ng/ml). 1 µl of control skeletal muscle cDNA (from the *Rsa* I Digestion) was then mixed with 5 µl of the diluted ϕX174/ *Hae* III DNA (150 ng/ml) in order to produce the control skeletal muscle tester cDNA.

Preparation of the adaptor-ligated tester cDNA

[0107] A ligation master mix was prepared by combining 3 µl of sterile water, 2 µl of 5X ligation buffer and 1 µl T4 DNA ligase (400 units/µl) per reaction. 2 µl of adaptor 1 (10 µM) was then added to 2 µl of the diluted tester cDNA. To this, 6 µl of the ligation master mix was also added. The tube was therefore labeled Tester 1-1. In a separate tube, 2 µl of the adaptor 2R (10 µM) was mixed with 2 µl of the diluted tester cDNA and 6 µl of the master mix. This tube was named Tester 1-2.

[0108] 2 µl of Tester 1-1 and 2 µl of Tester 1-2 were then placed into fresh tubes. These would later be used as the unsubtracted tester control. The remainder of the contents of Tester 1-1 and Tester 1-2 tubes were then centrifuged briefly and incubated at 16°C overnight. The ligation reaction was stopped by adding 1 µl of EDTA/glycogen mix and the samples were heated at 72°C for 5 min in order to inactivate the ligase. In doing so, preparation of the experimental and control skeletal muscle adaptor-ligated tester cDNAs was complete.

[0109] 1 µl from each unsubtracted tester control was then removed and diluted into 1 ml of water. These samples were set aside as they were to be used later for PCR (see below). All of the samples were stored at -20°C

Analysis of Ligation efficiency

[0110] 1 µl of each ligated cDNA was diluted into 200 µl of water and the following reagents were then combined in four separate tubes:

Component	Tube:	1	2	3	4
Tester 1-1 (ligated to Adaptor 1)		1	1	-	-
Tester 1-2 (ligated to Adaptor 2R)		-	-	1	1
G3PDH 3' primer (10 µM)		1	1	1	1
G3PDH 5' primer (10 µM)		-	1	-	1
PCR primer 1 (10 µM)		1	-	1	-
Total volume µl		3	3	3	3

[0111] A master mix for all of the reaction tubes plus one additional tube was made up by adding 18.5 µl of sterile H_2O, 2.5 µl of 10X PCR reaction buffer, 0.5 µl of dNTP mix (10 mM), and 0.5 µl of 50X Advantage cDNA Polymerase Mix, per reaction, into a fresh tube. 22 µl of this master mix was then aliquotted into each of the 4 reaction tubes prepared above. The contents of the tubes were overlaid with 50 µl of mineral oil. The reaction mix was incubated in a thermal cycler at 75°C for 5 min in order to extend the adaptors. The following protocol was then carried out immediately in a thermal cycler (Perkin-Elmer GeneAmp PCR Systems 2400): 94°C for 30 sec (1 cycle), 94°C 10 sec, 65°C 30 sec and then 68°C 2.5 min (25 cycles)

First Hybridisation

[0112] 1.5 µl of the Adaptor 1-ligated Tester 1-1 was combined with 1.5 µl of the *Rsa* I-digested driver cDNA, prepared earlier and 1 µl of 4X Hybridisation buffer. This process was then repeated combining the Adaptor 2R-ligated Tester 1-2 with the *Rsa* I-digested driver cDNA and 4X hybridisation buffer. The samples were incubated in a thermal cycler at 98°C for 1.5 min followed by incubation at 68°C for 8 hr.

Second Hybridisation

[0113] 1 µl of Driver cDNA (i.e. the *Rsa* I-digested cDNA (see above)), 1 µl 4X Hybridisation buffer and 2 µl Sterile H_2O were all combined in a fresh tube. 1 µl of this mix was then removed and placed in a new tube, overlaid with 1 drop of mineral oil and incubated at 98°C for 1.5 min in order to denature the driver. The following procedure was used to simultaneously mix the driver with hybridisation samples 1 and 2 (prepared in the first hybridisation), thus ensuring that the two hybridisation samples were mixed together only in the presence of freshly denatured driver: A micropipettor was set at 15 µl. The pipette tip was then touched onto the mineral oil/sample interface of the tube containing hybridisation sample 2. The entire sample was drawn partway into the tip before it was removed from the tube in order to draw a small amount of air into the tip. The pipette tip was then touched onto the interface of the tube containing the freshly denatured driver (i.e. the tip contained both samples separated by a small pocket of air) before the entire mixture was transferred to the tube containing hybridisation sample 1. The reaction was then incubated at 68°C overnight. 200 µl of dilution buffer was added to the tube, which was then heated in a thermal cycler at 68°C for 7 min. The product of this second hybridisation was stored at -20°C.

PCR Amplification

[0114] Seven PCR reactions were set up: (1) The forward-subtracted experimental cDNA, (2) the unsubtracted tester control (see preparation of the adaptor ligated tester cDNA), (3) the reverse-subtracted experimental cDNA, (4) the unsubtracted tester control for the reverse subtraction, (5) the subtracted control skeletal muscle cDNA, (6) the unsubtracted tester control for the control subtraction, and (7) the PCR control subtracted cDNA (provided in the kit). The PCR control subtracted cDNA was required to provide a positive PCR control as it contained a successfully subtracted mixture of *Hae* III-digested ϕX174 DNA.

[0115] The PCR templates were prepared by aliquotting 1 µl of each diluted cDNA (i.e., each subtracted sample from the second hybridisation and the corresponding diluted unsubtracted tester control produced by the adaptor ligation see above) into an appropriately labeled tube. 1 µl of the PCR control subtracted cDNA was placed into a fresh tube. A master mix for all of the primary PCR tubes, plus one additional reaction, was then prepared by combining 19.5 µl of sterile water, 2.5 µl of 10X PCR reaction buffer, 0.5 µl of dNTP Mix (10 mM), 1.0 µl of PCR primer 1 (10 µM)

and 0.5 µl of 50X Advantage cDNA Polymerase Mix. 24 µl of Master Mix was then aliquotted into each of the 7 reaction tubes prepared above and the mixture was overlaid with 50 µl of mineral oil, before being incubated in a thermal cycler at 75°C for 5 min in order to extend the adaptors. Thermal cycling was then immediately started using the following protocol: 94°C 25 sec (1 cycle), 94°C 10 sec, 66°C 30 sec and 72°C 1.5 min (32 cycles).

[0116] 3 µl of each primary PCR mixture was then diluted in 27 µl of H_2O, 1 µl of each of these dilutions was then placed into a fresh tube.

[0117] A master mix for the secondary PCRs, (plus an additional reaction) was set up by combining 18.5 µl of sterile water, 2.5 µl of 10X PCR reaction buffer, 1.0 µl of Nested PCR primer 1 (10 µM), 1.0 µl of Nested PCR primer 2R (10 µM), 0.5 µl of dNTP Mix (10 mM) and 0.5 µl of 50X Advantage cDNA Polymerase Mix per reaction. 24 µl of this Master Mix was then added into each reaction tube containing the 1 µl diluted primary PCR mixture. The following PCR protocol was then carried out: 94°C 10 sec, 68°C 30 sec and 72°C 1.5 min (12 cycles). The reaction products were then stored at -20°C.

Ligation into a Vector/ Transformation & PCR

[0118] The products of the PCR amplification (enriched for differentially expressed cDNAs) were ligated into the pCR2.1-TOPO vector using a T/A cloning kit (Invitrogen), transformed into TOPO One Shot competent cells according to the manufacturers protocol and grown up on LB (Luria-Bertani) Agar plates overnight at 37°C. 1,000 colonies were then individually picked (using fresh sterile tips) and dipped into 5 µl of sterile water which had been aliquotted previously into 96 well PCR plates. The water/colonies were heated in a thermal cycler at 100°C for 10 minutes in order to burst the cells, thus releasing the plasmids containing a differentially expressed cDNA insert. The 5 µl of water/plasmid was then used as a template in a PCR reaction (see below) using M13 Forward and Reverse primers (10 ng/µl), complementary to the M13 site present on either side of the cloning site on the vector. 5 µl of the PCR product was then run on a 2% agarose gel and stained by ethidium bromide. PCR products of an amplified insert were identified and 5 µl of the remainder of the PCR product (i.e. from the 15 µl that had not been run on the gel) was diluted 1/10 with water. 5 µl of the diluted PCR product was then used as a template in a sequencing reaction.

Sequencing

[0119] A sequencing reaction containing M13 primer (3.2 pmol/µl), 'BigDye' reaction mix (i.e. AmpliTaq® DNA polymerase, $MgCl_2$, buffer and fluorescent dNTPs [each of the four deoxynucleoside triphosphates is linked to a specific fluorescent donor dye which in turn is attached to a specific acceptor dye]) and cDNA template (diluted PCR product) was set up. The reaction was carried out on a thermal cycler for 25 cycles of 10 seconds at 96°C, 20 seconds at 50°C and 4 minutes at 60°C. Each reaction product was then purified through a hydrated Centri-Sep column, and lyophilised. The pellets were resuspended in Template Supression Reagent and sequenced on an ABI Prism 310 Genetic Analyser. The analyser uses an ion laser to excite the specific donor dye that transfers its energy to the acceptor dye, which emits a specific energy spectrum that can be read by the sequencer.

[0120] The differentially expressed genes of the streptozocin-induced diabetes experiment and of the CCI experiment were sequenced at Parke-Davis, Cambridge and at the applicant's core sequencing facility in Ann Arbor, MI, USA.

Bioinformatics

[0121] The sequencing results were analysed using the computer program CHROMAS in which the vector and adaptor sequences were clipped off, leaving only the nucleotide sequence of the differentially expressed gene. Each sequence was then checked for homology to known genes, Expressed Sequence Tags (ESTs) and Proteins using various Basic Local Alignment Search Tool (BLAST) searches against the Genbank sequence database at the National Centre for Biotechnology Information, Bethesda, Maryland, USA (NCBI).

[0122] Lists were derived called STZup and STZdown and CCIup and CCIdown that contain the nucleic acid sequences from the forward and back subtracted libraries respectively. In each list there are given accession numbers and descriptions for the known rat genes identified, and where available corresponding mouse or human genes. Sequences that are considered to be of interest and that are down-regulated both in a streptozocin-induced diabetes model and in a chronic constrictive injury pain model are identified in Tables I - VI above and are listed below.

[0123] References have been given where available for the sequences that have been found, and sequence listings have been given in the form in which they currently appear in publicly searchable databases e.g. the NCBI databaase (National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, Maryland, MD 20894, USA, www.ncbi.nlm.nih.gov). These sequence listings are given for the purposes of identification only. The invention includes the use of subsequently revised versions of the above sequences (which may incorporate small differences to the version set out herein) and homologous sequences or similar proteins in other species as

determined by a high percentage identity (e.g. above 50%, preferably above 90%), length of alignment and functional equivalence.

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SEQUENCE LISTING

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Ile Leu Ser Thr Leu Leu Gly Asn Thr Leu Val Cys Ala Ala Val Ile
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Arg Phe Arg His Leu Arg Ser Lys Val Thr Asn Phe Phe Val Ile Ser
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Leu Ala Val Ser Asp Leu Leu Val Ala Val Leu Val Met Pro Trp Lys
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Ala Val Ala Glu Ile Ala Gly Phe Trp Pro Phe Gly Ser Phe Cys Asn
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Ile Trp Val Ala Phe Asp Ile Met Cys Ser Thr Ala Ser Ile Leu Asn
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Leu Cys Val Ile Ser Val Asp Arg Tyr Trp Ala Ile Ser Ser Pro Phe
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Gln Tyr Glu Arg Lys Met Thr Pro Lys Ala Ala Phe Ile Leu Ile Ser
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Val Ala Trp Thr Leu Ser Val Leu Ile Ser Phe Ile Pro Val Gln Leu
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Ser Trp His Lys Ala Lys Pro Thr Trp Pro Leu Asp Gly Asn Phe Thr
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Ile Met Ile Val Thr Tyr Thr Ser Ile Tyr Arg Ile Ala Gln Lys Gln
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Ile Arg Arg Ile Ser Ala Leu Glu Arg Ala Ala Val His Ala Lys Asn
225                 230                 235                 240

Cys Gln Thr Thr Ala Gly Asn Gly Asn Pro Val Glu Cys Ala Gln Ser
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Glu Ser Ser Phe Lys Met Ser Phe Lys Arg Glu Thr Lys Val Leu Lys
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Thr Leu Ser Val Ile Met Gly Val Phe Val Cys Cys Trp Leu Pro Phe
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Phe Ile Ser Asn Cys Met Val Pro Phe Cys Gly Ser Glu Glu Thr Gln
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Pro Phe Cys Ile Asp Ser Ile Thr Phe Asp Val Phe Val Trp Phe Gly
305                 310                 315                 320

Trp Ala Asn Ser Ser Leu Asn Pro Ile Ile Tyr Ala Phe Asn Ala Asp
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Phe Gln Lys Ala Phe Ser Thr Leu Leu Gly Cys Tyr Arg Leu Cys Pro
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Thr Thr Asn Asn Ala Ile Glu Thr Val Ser Ile Asn Asn Asn Gly Ala
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Val Val Phe Ser Ser His His Glu Pro Arg Gly Ser Ile Ser Lys Asp
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Cys Asn Leu Val Tyr Leu Ile Pro His Ala Val Gly Ser Ser Glu Asp
385                 390                 395                 400

Leu Lys Lys Glu Glu Ala Gly Gly Ile Ala Lys Pro Leu Glu Lys Leu
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Ser Pro Ala Leu Ser Val Ile Leu Asp Tyr Asp Thr Asp Val Ser Leu
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Glu Lys Ile Gln Pro Val Thr His Ser Gly Gln His Ser Thr
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His Pro Pro Trp Glu Gly Gly Ile Arg Tyr Arg Gly Leu Ile Arg Asp
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Gln Val Lys Ala Ile Asn Phe Leu Pro Val Asp Tyr Glu Ile Glu Tyr
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Val Cys Arg Gly Glu Arg Glu Val Val Gly Pro Lys Val Arg Lys Cys
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Arg Ile Cys Ser Lys Ser Tyr Leu Thr Leu Glu Asn Gly Lys Val Phe
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Ser Gln Gly Gln Trp Ser Thr Pro Lys Pro His Cys Gln Val Asn Arg
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Thr Pro His Ser Glu Arg Arg Ala Val Tyr Ile Gly Ala Leu Phe Pro
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Met Ser Gly Gly Trp Pro Gly Gly Gln Ala Cys Gln Pro Ala Val Glu
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Met Ala Leu Glu Asp Val Asn Ser Arg Arg Asp Ile Leu Pro Asp Tyr
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Glu Leu Lys Leu Ile His His Asp Ser Lys Cys Asp Pro Gly Gln Ala
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Thr Lys Tyr Leu Tyr Glu Leu Leu Tyr Asn Asp Pro Ile Lys Ile Ile
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Ala Thr Leu His Asn Pro Thr Arg Val Lys Leu Phe Glu Lys Trp Gly
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Trp Lys Lys Ile Ala Thr Ile Gln Gln Thr Thr Glu Val Phe Thr Ser
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Thr Leu Asp Asp Leu Glu Glu Arg Val Lys Glu Ala Gly Ile Glu Ile
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Thr Phe Arg Gln Ser Phe Phe Ser Asp Pro Ala Val Pro Val Lys Asn
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Leu Lys Arg Gln Asp Ala Arg Ile Ile Val Gly Leu Phe Tyr Glu Thr
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Glu Ala Arg Lys Val Phe Cys Glu Val Tyr Lys Glu Arg Leu Phe Gly
    370                 375                 380

Lys Lys Tyr Val Trp Phe Leu Ile Gly Trp Tyr Ala Asp Asn Trp Phe
385                 390                 395                 400

Lys Thr Tyr Asp Pro Ser Ile Asn Cys Thr Val Glu Glu Met Thr Glu
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Ala Val Glu Gly His Ile Thr Thr Glu Ile Val Met Leu Asn Pro Ala
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Asn Thr Arg Ser Ile Ser Asn Met Thr Ser Gln Glu Phe Val Glu Lys
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Leu Thr Lys Arg Leu Lys Arg His Pro Glu Glu Thr Gly Gly Phe Gln
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Glu Ala Pro Leu Ala Tyr Asp Ala Ile Trp Ala Leu Ala Leu Ala Leu
465                 470                 475                 480

Asn Lys Thr Ser Gly Gly Gly Gly Arg Ser Gly Val Arg Leu Glu Asp
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Phe Asn Tyr Asn Asn Gln Thr Ile Thr Asp Gln Ile Tyr Arg Ala Met
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Asn Ser Ser Ser Phe Glu Gly Val Ser Gly His Val Val Phe Asp Ala
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Ser Gly Ser Arg Met Ala Trp Thr Leu Ile Glu Gln Leu Gln Gly Gly
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Ser Tyr Lys Lys Ile Gly Tyr Tyr Asp Ser Thr Lys Asp Asp Leu Ser
545                 550                 555                 560

Trp Ser Lys Thr Asp Lys Trp Ile Gly Gly Ser Pro Pro Ala Asp Gln
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Thr Leu Val Ile Lys Thr Phe Arg Phe Leu Ser Gln Lys Leu Phe Ile
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Ser Val Ser Val Leu Ser Ser Leu Gly Ile Val Leu Ala Val Val Cys
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Leu Ser Phe Asn Ile Tyr Asn Ser His Ala Arg Tyr Ile Gln Asn Ser
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Gln Pro Asn Leu Asn Asn Leu Thr Ala Val Gly Cys Ser Leu Ala Leu
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Ala Val Val Phe Pro Leu Gly Leu Asp Gly Tyr His Ile Gly Arg Ser
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Gln Phe Pro Phe Val Cys Gln Ala Arg Leu Trp Leu Leu Gly Leu Gly
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Phe Ser Leu Gly Tyr Gly Ser Met Phe Thr Lys Ile Trp Trp Val His
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Thr Val Phe Thr Lys Lys Glu Glu Lys Lys Glu Trp Arg Lys Thr Leu
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Glu Pro Trp Lys Leu Tyr Ala Thr Val Gly Leu Leu Val Gly Met Asp
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Val Leu Thr Leu Ala Ile Trp Gln Ile Val Asp Pro Leu His Arg Thr
725 730 735

Ile Glu Thr Phe Ala Lys Glu Glu Pro Lys Glu Asp Ile Asp Val Ser
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Ile Leu Pro Gln Leu Glu His Cys Ser Ser Lys Lys Met Asn Thr Trp
755 760 765

Leu Gly Ile Phe Tyr Gly Tyr Lys Gly Leu Leu Leu Leu Leu Gly Ile
770 775 780

Phe Leu Ala Tyr Glu Thr Lys Ser Val Ser Thr Glu Lys Ile Asn Asp
785 790 795 800

His Arg Ala Val Gly Met Ala Ile Tyr Asn Val Ala Val Leu Cys Leu
805 810 815

Ile Thr Ala Pro Val Thr Met Ile Leu Ser Ser Gln Gln Asp Ala Ala
820 825 830

Phe Ala Phe Ala Ser Leu Ala Ile Val Phe Ser Ser Tyr Ile Thr Leu
835 840 845

Val Val Leu Phe Val Pro Lys Met Arg Arg Leu Ile Thr Arg Gly Glu
850 855 860

Trp Gln Ser Glu Thr Gln Asp Thr Met Lys Thr Gly Ser Ser Thr Asn
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Asn Asn Glu Glu Glu Lys Ser Arg Leu Leu Glu Lys Glu Asn Arg Glu
885 890 895

Leu Glu Lys Ile Ile Ala Glu Lys Glu Glu Arg Val Ser Glu Leu Arg
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His Gln Leu Gln Ser Arg Gln Gln Leu Arg Ser Arg Arg His Pro Pro
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Thr Pro Pro Asp Pro Ser Gly Gly Leu Pro Arg Gly Pro Ser Glu Pro
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Pro Asp Arg Leu Ser Cys Asp Gly Ser Arg Val His Leu Leu Tyr Lys
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<210> 6
<211> 4365

<212> DNA
<213> Mus musculus

<220>
<223> GABA-B1a receptor

<400> 6

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<210> 7
<211> 582
<212> PRT
<213> Rattus norvegicus

<220>
<223> Differentiation-associated Na-dependent inorganic phosphate cotransporter

<400> 7

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Lys Lys Gln Asp Asn Arg Glu Thr Ile Glu Leu Thr Glu Asp Gly Lys
35 40 45

Pro Leu Glu Val Pro Glu Lys Lys Ala Pro Leu Cys Asp Cys Thr Cys
50 55 60

Phe Gly Leu Pro Arg Arg Tyr Ile Ile Ala Ile Met Ser Gly Leu Gly
65 70 75 80

Phe Cys Ile Ser Phe Gly Ile Arg Cys Asn Leu Gly Val Ala Ile Val
85 90 95

Asp Met Val Asn Asn Ser Thr Ile His Arg Gly Gly Lys Val Ile Lys
100 105 110

Glu Lys Ala Lys Phe Asn Trp Asp Pro Glu Thr Val Gly Met Ile His
115 120 125

Gly Ser Phe Phe Trp Gly Tyr Ile Ile Thr Gln Ile Pro Gly Gly Tyr
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Ile Ala Ser Arg Leu Ala Ala Asn Arg Val Phe Gly Ala Ala Ile Leu
145 150 155 160

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Leu Thr Ser Thr Leu Asn Met Leu Ile Pro Ser Ala Ala Arg Val His
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Tyr Gly Cys Val Ile Phe Val Arg Ile Leu Gln Gly Leu Val Glu Gly
            180                 185                 190

Val Thr Tyr Pro Ala Cys His Gly Ile Trp Ser Lys Trp Ala Pro Pro
        195                 200                 205

Leu Glu Arg Ser Arg Leu Ala Thr Thr Ser Phe Cys Gly Ser Tyr Ala
    210                 215                 220

Gly Ala Val Ile Ala Met Pro Leu Ala Gly Ile Leu Val Gln Tyr Thr
225                 230                 235                 240

Gly Trp Ser Ser Val Phe Tyr Val Tyr Gly Ser Phe Gly Met Val Trp
                245                 250                 255

Tyr Met Phe Trp Leu Leu Val Ser Tyr Glu Ser Pro Ala Lys His Pro
            260                 265                 270

Thr Ile Thr Asp Glu Glu Arg Arg Tyr Ile Glu Glu Ser Ile Gly Glu
        275                 280                 285

Ser Ala Asn Leu Leu Gly Ala Met Glu Lys Phe Lys Thr Pro Trp Arg
    290                 295                 300

Lys Phe Phe Thr Ser Met Pro Val Tyr Ala Ile Ile Val Ala Asn Phe
305                 310                 315                 320

Cys Arg Ser Trp Thr Phe Tyr Leu Leu Leu Ile Ser Gln Pro Ala Tyr
                325                 330                 335

Phe Glu Glu Val Phe Gly Phe Glu Ile Ser Lys Val Gly Met Leu Ser
            340                 345                 350

Ala Val Pro His Leu Val Met Thr Ile Ile Val Pro Ile Gly Gly Gln
        355                 360                 365

Ile Ala Asp Phe Leu Arg Ser Lys Gln Ile Leu Ser Thr Thr Thr Val
    370                 375                 380

Arg Lys Ile Met Asn Cys Gly Gly Phe Gly Met Glu Ala Thr Leu Leu
385                 390                 395                 400

Leu Val Val Gly Tyr Ser His Thr Arg Gly Val Ala Ile Ser Phe Leu
                405                 410                 415

Val Leu Ala Val Gly Phe Ser Gly Phe Ala Ile Ser Gly Phe Asn Val
            420                 425                 430

Asn His Leu Asp Ile Ala Pro Arg Tyr Ala Ser Ile Leu Met Gly Ile
        435                 440                 445

Ser Asn Gly Val Gly Thr Leu Ser Gly Met Val Cys Pro Ile Ile Val
    450                 455                 460

Gly Ala Met Thr Lys Asn Lys Ser Arg Glu Glu Trp Gln Tyr Val Phe
465                 470                 475                 480

Leu Ile Ala Ala Leu Val His Tyr Gly Gly Val Ile Phe Tyr Ala Leu
                485                 490                 495
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Phe Ala Ser Gly Glu Lys Gln Pro Trp Ala Asp Pro Glu Glu Thr Ser
500 505 510

Glu Glu Lys Cys Gly Phe Ile His Glu Asp Glu Leu Asp Glu Glu Thr
515 520 525

Gly Asp Ile Thr Gln Asn Tyr Ile Asn Tyr Gly Thr Thr Lys Ser Tyr
530 535 540

Gly Ala Thr Ser Gln Glu Asn Gly Gly Trp Pro Asn Gly Trp Glu Lys
545 550 555 560

Lys Glu Glu Phe Val Gln Glu Ser Ala Gln Asp Ala Tyr Ser Tyr Lys
565 570 575

Asp Arg Asp Asp Tyr Ser
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<210> 8
<211> 3982
<212> DNA
<213> Rattus norvegicus

<220>
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<213> Homo sapiens

<220>
<223> Vacuolar assembly protein VSP41 gene

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Glu Arg Leu Ser Asn Gly Val Thr Glu Ile Leu Gln Lys Asp Ala Ala
         35                  40                  45

Ser Cys Met Thr Val His Asp Lys Phe Leu Ala Leu Gly Thr His Tyr
     50                  55                  60

Gly Lys Val Tyr Leu Leu Asp Val Gln Gly Asn Ile Thr Gln Lys Phe
 65                  70                  75                  80
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Asp Val Ser Pro Val Lys Ile Asn Gln Ile Ser Leu Asp Glu Ser Gly
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Glu His Met Gly Val Cys Ser Glu Asp Gly Lys Val Gln Val Phe Gly
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Leu Tyr Ser Gly Glu Glu Phe His Glu Thr Phe Asp Cys Pro Ile Lys
        115                 120                 125

Ile Ile Ala Val His Pro His Phe Val Arg Ser Ser Cys Lys Gln Phe
    130                 135                 140

Val Thr Gly Gly Lys Lys Leu Leu Leu Phe Glu Arg Ser Trp Met Asn
145                 150                 155                 160

Arg Trp Lys Ser Ala Val Leu His Glu Gly Glu Gly Asn Ile Arg Ser
                165                 170                 175

Val Lys Trp Arg Gly His Leu Ile Ala Trp Ala Asn Asn Met Gly Val
            180                 185                 190

Lys Ile Phe Asp Ile Ile Ser Lys Gln Arg Ile Thr Asn Val Pro Arg
        195                 200                 205

Asp Asp Ile Ser Leu Arg Pro Asp Met Tyr Pro Cys Ser Leu Cys Trp
    210                 215                 220

Lys Asp Asn Val Thr Leu Ile Ile Gly Trp Gly Thr Ser Val Lys Val
225                 230                 235                 240

Cys Ser Val Lys Glu Arg His Ala Ser Glu Met Arg Asp Leu Pro Ser
                245                 250                 255

Arg Tyr Val Glu Ile Val Ser Gln Phe Glu Thr Glu Phe Tyr Ile Ser
            260                 265                 270

Gly Leu Ala Pro Leu Cys Asp Gln Leu Val Val Leu Ser Tyr Val Lys
        275                 280                 285

Glu Ile Ser Glu Lys Thr Glu Arg Glu Tyr Cys Ala Arg Pro Arg Leu
    290                 295                 300

Asp Ile Ile Gln Pro Leu Ser Glu Thr Cys Glu Glu Ile Ser Ser Asp
305                 310                 315                 320

Ala Leu Thr Val Arg Gly Phe Gln Glu Asn Glu Cys Arg Asp Tyr His
                325                 330                 335

Leu Glu Tyr Ser Glu Gly Glu Ser Leu Phe Tyr Ile Val Ser Pro Arg
            340                 345                 350

Asp Val Val Val Ala Lys Glu Arg Asp Gln Asp Asp His Ile Asp Trp
        355                 360                 365

Leu Leu Glu Lys Lys Lys Tyr Glu Glu Ala Leu Met Ala Ala Glu Ile
    370                 375                 380

Ser Gln Lys Asn Ile Lys Arg His Lys Ile Leu Asp Ile Gly Leu Ala
385                 390                 395                 400

Tyr Ile Asn His Leu Val Glu Arg Gly Asp Tyr Asp Ile Ala Ala Arg
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405 410 415

Lys Cys Gln Lys Ile Leu Gly Lys Asn Ala Ala Leu Trp Glu Tyr Glu
420 425 430

Val Tyr Lys Phe Lys Glu Ile Gly Gln Leu Lys Ala Ile Ser Pro Tyr
435 440 445

Leu Pro Arg Gly Asp Pro Val Leu Lys Pro Leu Ile Tyr Glu Met Ile
450 455 460

Leu His Glu Phe Leu Glu Ser Asp Tyr Glu Gly Phe Ala Thr Leu Ile
465 470 475 480

Arg Glu Trp Pro Gly Asp Leu Tyr Asn Asn Ser Val Ile Val Gln Ala
485 490 495

Val Arg Asp His Leu Lys Lys Asp Ser Gln Asn Lys Thr Leu Leu Lys
500 505 510

Thr Leu Ala Glu Leu Tyr Thr Tyr Asp Lys Asn Tyr Gly Asn Ala Leu
515 520 525

Glu Ile Tyr Leu Thr Leu Arg His Lys Asp Val Phe Gln Leu Ile His
530 535 540

Lys His Asn Leu Phe Ser Ser Ile Lys Asp Lys Ile Val Leu Leu Met
545 550 555 560

Asp Phe Asp Ser Glu Lys Ala Val Asp Met Leu Leu Asp Asn Glu Asp
565 570 575

Lys Ile Ser Ile Lys Lys Val Val Glu Glu Leu Glu Asp Arg Pro Glu
580 585 590

Leu Gln His Val Tyr Leu His Lys Leu Phe Lys Arg Asp His His Lys
595 600 605

Gly Gln Arg Tyr His Glu Lys Gln Ile Ser Leu Tyr Ala Glu Tyr Asp
610 615 620

Arg Pro Asn Leu Leu Pro Phe Leu Arg Asp Ser Thr His Cys Pro Leu
625 630 635 640

Glu Lys Ala Leu Glu Ile Cys Gln Gln Arg Asn Phe Val Glu Glu Thr
645 650 655

Val Tyr Leu Leu Ser Arg Met Gly Asn Ser Arg Ser Ala Leu Lys Met
660 665 670

Ile Met Glu Glu Leu His Asp Val Asp Lys Ala Ile Glu Phe Ala Lys
675 680 685

Glu Gln Asp Asp Gly Glu Leu Trp Glu Asp Leu Ile Leu Tyr Ser Ile
690 695 700

Asp Lys Pro Pro Phe Ile Thr Gly Leu Leu Asn Asn Ile Gly Thr His
705 710 715 720

Val Asp Pro Ile Leu Leu Ile His Arg Ile Lys Glu Gly Met Glu Ile
725 730 735

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Pro Asn Leu Arg Asp Ser Leu Val Lys Ile Leu Gln Asp Tyr Asn Leu
            740                 745                 750

Gln Ile Leu Leu Arg Glu Gly Cys Lys Lys Ile Leu Val Ala Asp Ser
        755                 760                 765

Leu Ser Leu Leu Lys Lys Met His Arg Thr Gln Met Lys Gly Val Leu
    770                 775                 780

Val Asp Glu Glu Asn Ile Cys Glu Ser Cys Leu Ser Pro Ile Leu Pro
785                 790                 795                 800

Ser Asp Ala Ala Lys Pro Phe Ser Val Val Val Phe His Cys Arg His
                805                 810                 815

Met Phe His Lys Glu Cys Leu Pro Met Pro Ser Met Asn Ser Ala Ala
            820                 825                 830

Gln Phe Cys Asn Ile Cys Ser Ala Lys Asn Arg Gly Pro Gly Ser Ala
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Ile Leu Glu Met Lys Lys
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<211> 770
<212> PRT
<213> Rattus norvegicus

<220>
<223> Git 1

<400> 10

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Pro Asp Pro Gly Trp Ala Ser Ile Ser Arg Gly Val Leu Val Cys Asp
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Glu Cys Cys Ser Val His Arg Ser Leu Gly Arg His Ile Ser Ile Val
        35                  40                  45

Lys His Leu Arg His Ser Ala Trp Pro Pro Thr Leu Leu Gln Met Val
    50                  55                  60

His Thr Leu Ala Ser Asn Gly Ala Asn Ser Ile Trp Glu His Ser Leu
65                  70                  75                  80

Leu Asp Pro Ala Gln Val Gln Ser Gly Arg Arg Lys Ala Asn Pro Gln
                85                  90                  95

Asp Lys Val His Pro Ile Lys Ser Glu Phe Ile Arg Ala Lys Tyr Gln
            100                 105                 110

Met Leu Ala Phe Val His Lys Leu Pro Cys Arg Asp Asp Asp Gly Val
        115                 120                 125

Thr Ala Lys Asp Leu Ser Lys Gln Leu His Ser Ser Val Arg Thr Gly
    130                 135                 140

Asn Leu Glu Thr Cys Leu Arg Leu Leu Ser Leu Gly Ala Gln Ala Asn
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Phe Phe His Pro Glu Lys Gly Thr Thr Pro Leu His Val Ala Ala Lys
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Ala Gly Gln Thr Leu Gln Ala Glu Leu Leu Val Val Tyr Gly Ala Asp
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Pro Gly Ser Pro Asp Val Asn Gly Arg Thr Pro Ile Asp Tyr Ala Arg
        195                 200                 205

Gln Ala Gly His His Glu Leu Ala Glu Arg Leu Val Glu Cys Gln Tyr
    210                 215                 220

Glu Leu Thr Asp Arg Leu Ala Phe Tyr Leu Cys Gly Arg Lys Pro Asp
225                 230                 235                 240

His Lys Asn Gly His Tyr Ile Ile Pro Gln Met Ala Asp Arg Ser Arg
                245                 250                 255

Gln Lys Cys Met Ser Gln Ser Leu Asp Leu Ser Glu Leu Ala Lys Ala
            260                 265                 270

Ala Lys Lys Lys Leu Gln Ala Leu Ser Asn Arg Leu Phe Glu Glu Leu
        275                 280                 285

Ala Mct Asp Val Tyr Asp Glu Val Asp Arg Arg Glu Asn Asp Ala Val
    290                 295                 300

Trp Leu Ala Thr Gln Asn His Ser Thr Leu Val Thr Glu Arg Ser Ala
305                 310                 315                 320

Val Pro Phe Leu Pro Val Asn Pro Glu Tyr Ser Ala Thr Arg Asn Gln
                325                 330                 335

Gly Arg Gln Lys Leu Ala Arg Phe Asn Ala Arg Glu Phe Ala Thr Leu
            340                 345                 350

Ile Ile Asp Ile Leu Ser Glu Ala Lys Arg Arg Gln Gln Gly Lys Ser
        355                 360                 365

Leu Ser Ser Pro Thr Asp Asn Leu Glu Leu Ser Ala Arg Asn Gln Ser
    370                 375                 380

Asp Leu Asp Asp Gln His Asp Tyr Asp Ser Val Ala Ser Asp Glu Asp
385                 390                 395                 400

Thr Asp Gln Glu Pro Leu Pro Ser Ala Gly Ala Thr Arg Asn Asn Arg
                405                 410                 415

Ala Arg Ser Met Asp Ser Ser Asp Leu Ser Asp Gly Ala Val Thr Leu
            420                 425                 430

Gln Glu Tyr Leu Glu Leu Lys Lys Ala Leu Ala Thr Ser Glu Ala Lys
        435                 440                 445

Val Gln Gln Leu Met Lys Val Asn Ser Ser Leu Ser Asp Glu Leu Arg
    450                 455                 460

Lys Leu Gln Arg Glu Ile His Lys Leu Gln Ala Glu Asn Leu Gln Leu
465                 470                 475                 480
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Arg Gln Pro Pro Gly Pro Val Pro Val Pro Ser Leu Pro Ser Glu Arg
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Ala Glu His Thr Leu Met Gly Pro Gly Gly Ser Thr His Arg Arg Asp
500 505 510

Arg Gln Ala Phe Ser Met Tyr Glu Pro Gly Ser Ala Leu Lys Pro Phe
515 520 525

Gly Gly Ala Pro Gly Asp Glu Leu Ala Thr Arg Leu Gln Pro Phe His
530 535 540

Ser Thr Glu Leu Glu Asp Asp Ala Ile Tyr Ser Val His Val Pro Ala
545 550 555 560

Gly Leu Tyr Arg Ile Arg Lys Gly Val Ser Ala Ser Ser Val Thr Phe
565 570 575

Thr Pro Ser Ser Pro Leu Leu Ser Ser Ser Gln Glu Gly Ser Arg His
580 585 590

Ala Ser Lys Leu Ser Arg His Gly Ser Gly Ala Glu Ser Asp Tyr Glu
595 600 605

Asn Thr Gln Ser Gly Glu Pro Leu Leu Gly Leu Glu Gly Lys Arg Phe
610 615 620

Leu Glu Leu Ser Lys Glu Asp Glu Leu His Ala Glu Leu Glu Ser Leu
625 630 635 640

Asp Gly Asp Pro Asp Pro Gly Leu Pro Ser Thr Glu Asp Val Ile Leu
645 650 655

Lys Thr Glu Gln Val Thr Lys Asn Ile Gln Glu Leu Leu Arg Ala Ala
660 665 670

Gln Glu Phe Lys His Asp Ser Phe Val Pro Cys Ser Glu Lys Ile His
675 680 685

Leu Ala Val Thr Glu Met Ala Ser Leu Phe Pro Lys Arg Pro Ala Leu
690 695 700

Glu Pro Val Arg Ser Ser Leu Arg Leu Leu Asn Ala Ser Ala Tyr Arg
705 710 715 720

Leu Gln Ser Glu Cys Arg Lys Thr Val Pro Pro Glu Pro Gly Ala Pro
725 730 735

Val Asp Phe Gln Leu Leu Thr Gln Gln Val Ile Gln Cys Ala Tyr Asp
740 745 750

Ile Ala Lys Ala Ala Lys Gln Leu Val Thr Ile Thr Thr Arg Glu Lys
755 760 765

Lys Gln
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<212> DNA
<213> Rattus norvegicus

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<223> Git 1

<400> 11

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<212> PRT
<213> Homo sapiens

<220>
<223> Histone H3.3

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Pro Arg Lys Gln Leu Ala Thr Lys Ala Ala Arg Lys Ser Ala Pro Ser
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Thr Gly Gly Val Lys Lys Pro His Arg Tyr Arg Pro Gly Thr Val Ala
35 40 45

Leu Arg Glu Ile Arg Arg Tyr Gln Lys Ser Thr Glu Leu Leu Ile Arg
50 55 60

Lys Leu Pro Phe Gln Arg Leu Val Arg Glu Ile Ala Gln Asp Phe Lys
65 70 75 80

Thr Asp Leu Arg Phe Gln Ser Ala Ala Ile Gly Ala Leu Gln Glu Ala
85 90 95

Ser Glu Ala Tyr Leu Val Gly Leu Phe Glu Asp Thr Asn Leu Cys Ala
100 105 110

Ile His Ala Lys Arg Val Thr Ile Met Pro Lys Asp Ile Gln Leu Ala
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Arg Arg Ile Arg Gly Glu Arg Ala
130 135

<210> 13
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<212> DNA
<213> Homo sapiens

<220>
<223> Histone H3.3

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<211> 520
<212> PRT
<213> Rattus norvegicus

<220>
<223> Cytosolic 3-hydroxy 3-methylglutaryl coenzyme A synthase

<400> 14

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Val Gly Ile Val Ala Leu Glu Ile Tyr Phe Pro Ser Gln Tyr Val Asp
20 25 30

Gln Ala Glu Leu Glu Lys Tyr Asp Gly Val Asp Ala Gly Lys Tyr Thr
35 40 45

Ile Gly Leu Gly Gln Ala Arg Met Gly Phe Cys Thr Asp Arg Glu Asp
50 55 60

Ile Asn Ser Leu Cys Leu Thr Val Val Gln Lys Leu Met Glu Arg Asn
65 70 75 80

Ser Leu Ser Tyr Asp Cys Ile Gly Arg Leu Glu Val Gly Thr Glu Thr
85 90 95

Ile Ile Asp Lys Ser Lys Ser Val Lys Ser Asn Leu Met Gln Leu Phe
100 105 110

Glu Glu Ser Gly Asn Thr Asp Ile Glu Gly Ile Asp Thr Thr Asn Ala
115 120 125

Cys Tyr Gly Gly Thr Ala Ala Val Phe Asn Ala Val Asn Trp Ile Glu
130 135 140

Ser Ser Ser Trp Asp Gly Arg Tyr Ala Leu Val Val Ala Gly Asp Ile
145 150 155 160

Ala Ile Tyr Ala Ser Gly Asn Ala Arg Pro Thr Gly Gly Val Gly Ala
165 170 175

Val Ala Leu Leu Ile Gly Pro Asn Ala Pro Val Ile Phe Asp Arg Gly
180 185 190

Leu Arg Gly Thr His Met Gln His Ala Tyr Asp Phe Tyr Lys Pro Asp
195 200 205

Met Leu Ser Glu Tyr Pro Val Val Asp Gly Lys Leu Ser Ile Gln Cys
210 215 220

Tyr Leu Ser Ala Leu Asp Arg Cys Tyr Ser Val Tyr Arg Lys Lys Ile
225 230 235 240

Arg Ala Gln Trp Gln Lys Glu Gly Lys Asp Lys Asp Phe Thr Leu Asn

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Asp Phe Gly Phe Met Ile Phe His Ser Pro Tyr Cys Lys Leu Val Gln
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Lys Ser Leu Ala Arg Met Phe Leu Asn Asp Phe Leu Asn Asp Gln Asn
        275                 280                 285

Arg Asp Lys Asn Ser Ile Tyr Ser Gly Leu Glu Ala Phe Gly Asp Val
    290                 295                 300

Lys Leu Glu Asp Thr Tyr Phe Asp Arg Asp Val Glu Lys Ala Phe Met
305                 310                 315                 320

Lys Ala Ser Ala Glu Leu Phe Asn Gln Lys Thr Lys Ala Ser Leu Leu
                325                 330                 335

Val Ser Asn Gln Asn Gly Asn Met Tyr Thr Ser Ser Val Tyr Gly Ser
            340                 345                 350

Leu Ala Ser Val Leu Ala Gln Tyr Ser Pro Gln Gln Leu Ala Gly Lys
        355                 360                 365

Arg Ile Gly Val Phe Ser Tyr Gly Ser Gly Leu Ala Ala Thr Leu Tyr
    370                 375                 380

Scr Leu Lys Val Thr Gln Asp Ala Thr Pro Gly Ser Ala Leu Asp Lys
385                 390                 395                 400

Ile Thr Ala Ser Leu Cys Asp Leu Lys Ser Arg Leu Asp Ser Arg Thr
                405                 410                 415

Cys Val Ala Pro Asp Val Phe Ala Glu Asn Met Lys Leu Arg Glu Asp
            420                 425                 430

Thr His His Leu Ala Asn Tyr Ile Pro Gln Cys Ser Ile Asp Ser Leu
        435                 440                 445

Phe Glu Gly Thr Trp Tyr Leu Val Arg Val Asp Glu Lys His Arg Arg
    450                 455                 460

Thr Tyr Ala Arg Arg Pro Ser Thr Asn Asp His Ser Leu Asp Glu Gly
465                 470                 475                 480

Val Gly Leu Val His Ser Asn Thr Ala Thr Glu His Ile Pro Ser Pro
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Ala Lys Lys Val Pro Arg Leu Pro Ala Thr Ser Gly Glu Pro Glu Ser
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Ala Val Ile Ser Asn Gly Glu His
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<210> 15
<211> 3275
<212> DNA
<213> Rattus norvegicus

<220>
<223> Cytosolic 3-hydroxy 3-methylglutaryl coenzyme A synthase
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<400> 15

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atttttggtg ctgaactgac atgagcctca tagactgtaa aacagaggta gttgaaacta 2820
atgtacagaa ctacattttt taatttttatt tgcatttaat tctgtgaagt ttcagttatc 2880
taaaataaac acataaacgt gtaatgtttc agattgcaag gtgagatgta atgtagcatt 2940
tgtaagatat tcttgtcaat attaactggt aggattttga tttgtacagt tttaattggt 3000
taaaatgatc tcattttaac atccactgct atagatgaat gatgtaagct cagatttaat 3060
gaatggtggg gaaatggtgc atgtaatttt ttcgcaagta tcgagagttc tgtatgtttt 3120
gaaaagaata atttaacgtt tgggttgcca ggaagggggc tttcccagag tccattgcca 3180
ggcgttgggc aagcctcgca atgttggcac ggagcgttaa ccacacctta ctaatagcaa 3240
ggggaataac tttgaaataa agttttagac aaata 3275

<210> 16
<211> 353
<212> PRT

<213> Rattus norvegicus

<220>
<223> farnesyl pyrophosphate synthetase

<400> 16

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Met Asn Gly Asp Gln Lys Leu Asp Val His Asn Gln Glu Lys Gln Asn
  1               5                  10                  15

Phe Ile Gln His Phe Ser Gln Ile Val Lys Val Leu Thr Glu Asp Glu
             20                  25                  30

Leu Gly His Pro Glu Lys Gly Asp Ala Ile Thr Arg Ile Lys Glu Val
         35                  40                  45

Leu Glu Tyr Asn Thr Val Gly Gly Lys Tyr Asn Arg Gly Leu Thr Val
     50                  55                  60

Val Gln Thr Phe Gln Glu Leu Val Glu Pro Arg Lys Gln Asp Ala Glu
 65                  70                  75                  80

Ser Leu Gln Arg Ala Leu Thr Val Gly Trp Cys Val Glu Leu Leu Gln
                 85                  90                  95

Ala Phe Phe Leu Val Leu Asp Asp Ile Met Asp Ser Ser His Thr Arg
            100                 105                 110

Arg Gly Gln Ile Cys Trp Tyr Gln Lys Pro Gly Ile Gly Leu Asp Ala
        115                 120                 125

Ile Asn Asp Ala Leu Leu Leu Glu Ala Ala Ile Tyr Arg Leu Leu Lys
    130                 135                 140

Phe Tyr Cys Arg Glu Gln Pro Tyr Tyr Leu Asn Leu Leu Glu Leu Phe
145                 150                 155                 160

Leu Gln Ser Ser Tyr Gln Thr Glu Ile Gly Gln Thr Leu Asp Leu Ile
                165                 170                 175

Thr Ala Pro Gln Gly Gln Val Asp Leu Gly Arg Tyr Thr Glu Lys Arg
            180                 185                 190

Tyr Lys Ser Ile Val Lys Tyr Lys Thr Ala Phe Tyr Ser Phe Tyr Leu
        195                 200                 205

Pro Ile Ala Ala Ala Met Tyr Met Ala Gly Ile Asp Gly Glu Lys Glu
    210                 215                 220

His Ala Asn Ala Leu Lys Ile Leu Leu Glu Met Gly Glu Phe Phe Gln
225                 230                 235                 240

Ile Gln Asp Asp Tyr Leu Asp Leu Phe Gly Asp Pro Ser Val Thr Gly
                245                 250                 255

Lys Val Gly Thr Asp Ile Gln Asp Asn Lys Cys Ser Trp Leu Val Val
            260                 265                 270

Gln Cys Leu Leu Arg Ala Thr Pro Gln Gln Arg Gln Ile Leu Glu Glu
        275                 280                 285

Asn Tyr Gly Gln Lys Asp Pro Glu Lys Val Ala Arg Val Lys Ala Leu
    290                 295                 300
```

Tyr Glu Glu Leu Asp Leu Arg Ser Val Phe Phe Lys Tyr Glu Glu Asp
305 310 315 320

Ser Tyr Asn Arg Leu Lys Ser Leu Ile Glu Gln Cys Ser Ala Pro Leu
325 330 335

Pro Pro Ser Ile Phe Leu Glu Leu Ala Asn Lys Ile Tyr Lys Arg Arg
340 345 350

Lys

<210> 17
<211> 1271
<212> DNA
<213> Rattus norvegicus

<220>
<223> farnesyl pyrophosphate synthetase

<400> 17
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agcggatgca cgctctgctt ttaggtgtaa gccgcaaaca tcttggaccc cgggagaatc 120
cgcgttgaag cacagagcat ttagctcctc tgtcagaatg aatggggacc agaaactgga 180
tgttcataac caagaaaagc agaatttcat ccagcacttc tcccagattg tcaaggtgct 240
gactgaggat gaactgggac acccagagaa gggagatgct attacccgga tcaaagaggt 300
cctggagtac aacactgtag gaggcaagta caatcggggt ctgacggtgg tacagacctt 360
ccaggaactg gtggaaccaa ggaaacagga tgctgagagc ctacagcggg ccctgacggt 420
gggctggtgt gtagaactgc tccaggcttt cttcctcgtg ttagatgaca tcatggactc 480
ttcccacact cgccgggggc agatctgctg gtatcagaag ccgggcatag gcttggatgc 540
catcaacgat gctctgcttc tggaagccgc tatctaccgc ctgcttaagt tctactgcag 600
ggagcagccc tactacctca acctgctgga gctctttcta cagagttcct atcagactga 660
gatcgggcag actctcgacc tcatcacagc accccagggc caagtggatc ttggtagata 720
cactgaaaag aggtacaaat ctatcgtcaa gtacaagaca gctttctact ctttctacct 780
gcctatcgcg gctgccatgt acatggctgg aattgatggg gagaaggaac acgctaatgc 840
cctgaagatc ctgctggaga tgggcgagtt cttccagatc caggacgact accttgatct 900
ctttggagac cccagtgtga ccggaaaggt cggcactgac atccaggaca acaaatgcag 960
ctggctggtg gttcagtgtc tgctacgagc cactcctcag cagcgccaga tcttagagga 1020
gaattatggg cagaaggacc cagaaaaagt ggcgcgggtg aaagcactgt acgaggagct 1080
ggatctgcgg agtgtgttct tcaagtacga ggaagacagt tacaaccgcc tcaagagtct 1140
catagagcag tgctccgcgc ccctgccccc atccatcttc ctggaactag caaacaagat 1200
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<210> 18
<211> 152
<212> PRT
<213> Rattus norvegicus

<220>
<223> Bendless protein

<400> 18
Met Ala Gly Leu Pro Arg Arg Ile Ile Lys Glu Thr Gln Arg Leu Leu
1 5 10 15

Ala Glu Pro Val Pro Gly Ile Lys Ala Glu Pro Asp Glu Ser Asn Ala
20 25 30

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Arg Tyr Phe His Val Val Ile Ala Gly Pro Gln Asp Ser Pro Phe Glu
         35                  40                  45

Gly Gly Thr Phe Lys Leu Glu Leu Phe Leu Pro Glu Glu Tyr Pro Met
     50                  55                  60

Ala Ala Pro Lys Val Arg Phe Met Thr Lys Ile Tyr His Pro Asn Val
 65                  70                  75                  80

Asp Lys Leu Gly Arg Ile Cys Leu Asp Ile Leu Lys Asp Lys Trp Ser
                85                  90                  95

Pro Ala Leu Gln Ile Arg Thr Val Leu Leu Ser Ile Gln Ala Leu Leu
            100                 105                 110

Ser Ala Pro Asn Pro Asp Asp Pro Leu Ala Asn Asp Val Ala Glu Gln
        115                 120                 125

Trp Lys Ser Asn Glu Ala Gln Ala Ile Glu Thr Ala Arg Ala Trp Thr
    130                 135                 140

Arg Leu Tyr Ala Met Asn Asn Ile
145                 150
```

<210> 19
<211> 459
<212> DNA
<213> Rattus norvegicus

<220>
<223> Bendless protein

<400> 19
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cctggcatta aagcagaacc agatgagagc aacgcccgtt attttcatgt ggtcattgct 120
ggtccccagg attccccctt tgagggaggg acttttaaac ttgaactatt ccttccagaa 180
gaatacccaa tggcagcacc taaagtacgt ttcatgacca aaatttatca tcctaatgta 240
gacaagttgg gaagaatatg tttagatatt ttgaaagata agtggtcccc agcactgcag 300
atccgaacag ttctgctatc aatccaggct ttgctaagtg ctcctaatcc agatgatcca 360
ttagcaaatg atgtagctga gcagtggaag agcaacgaag cccaagccat agaaacagca 420
agagcatgga ctaggctata tgccatgaat aatatttaa 459

<210> 20
<211> 2505
<212> PRT
<213> Rattus norvegicus

<220>
<223> Fatty acid synthase

<400> 20
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Met Glu Glu Val Val Ile Ala Gly Met Ser Gly Lys Leu Pro Glu Ser
  1               5                  10                  15

Glu Asn Leu Gln Glu Phe Trp Ala Asn Leu Ile Gly Gly Val Asp Met
             20                  25                  30
```

```
Val Thr Asp Asp Asp Arg Arg Trp Lys Ala Gly Leu Tyr Gly Leu Pro
          35                  40                  45

Lys Arg Ser Gly Lys Leu Lys Asp Leu Ser Lys Phe Asp Ala Ser Phe
      50                  55                  60

Phe Gly Val His Pro Lys Gln Ala His Thr Met Asp Pro Gln Leu Arg
 65                  70                  75                  80

Leu Leu Leu Glu Val Ser Tyr Glu Ala Ile Val Asp Gly Gly Ile Asn
                 85                  90                  95

Pro Ala Ser Leu Arg Gly Thr Asn Thr Gly Val Trp Val Gly Val Ser
            100                 105                 110

Gly Ser Glu Ala Ser Glu Ala Leu Ser Arg Asp Pro Glu Thr Leu Leu
        115                 120                 125

Gly Tyr Ser Met Val Gly Cys Gln Arg Ala Met Met Ala Asn Arg Leu
    130                 135                 140

Ser Phe Phe Phe Asp Phe Lys Gly Pro Ser Ile Ala Leu Asp Thr Ala
145                 150                 155                 160

Cys Ser Ser Ser Leu Leu Ala Leu Gln Asn Ala Tyr Gln Ala Ile Arg
                165                 170                 175

Ser Gly Glu Cys Pro Ala Ala Ile Val Gly Gly Ile Asn Leu Leu Leu
            180                 185                 190

Lys Pro Asn Thr Ser Val Gln Phe Met Lys Leu Gly Met Leu Ser Pro
        195                 200                 205

Asp Gly Thr Cys Arg Ser Phe Asp Asp Ser Gly Asn Gly Tyr Cys Arg
    210                 215                 220

Ala Glu Ala Val Val Ala Val Leu Leu Thr Lys Lys Ser Leu Ala Arg
225                 230                 235                 240

Arg Val Tyr Ala Thr Ile Leu Asn Ala Gly Thr Asn Thr Asp Gly Cys
                245                 250                 255

Lys Glu Gln Gly Val Thr Phe Pro Ser Gly Glu Ala Gln Glu Gln Leu
            260                 265                 270

Ile Arg Ser Leu Tyr Gln Pro Gly Gly Val Ala Pro Glu Ser Leu Glu
        275                 280                 285

Tyr Ile Glu Ala His Gly Thr Gly Thr Lys Val Gly Asp Pro Gln Glu
    290                 295                 300

Leu Asn Gly Ile Thr Arg Ser Leu Cys Ala Phe Arg Gln Ser Pro Leu
305                 310                 315                 320

Leu Ile Gly Ser Thr Lys Ser Asn Met Gly His Pro Glu Pro Ala Ser
                325                 330                 335

Gly Leu Ala Ala Leu Thr Lys Val Leu Leu Ser Leu Glu Asn Gly Val
            340                 345                 350

Trp Ala Pro Asn Leu His Phe His Asn Pro Asn Pro Glu Ile Pro Ala
        355                 360                 365
```

```
Leu Leu Asp Gly Arg Leu Gln Val Val Asp Arg Pro Leu Pro Val Arg
    370                 375                 380

Gly Gly Ile Val Gly Ile Asn Ser Phe Gly Phe Gly Gly Ala Asn Val
385                 390                 395                 400

His Val Ile Leu Gln Pro Asn Thr Gln Gln Ala Pro Ala Pro Ala Pro
                405                 410                 415

His Ala Ala Leu Pro His Leu Leu His Ala Ser Gly Arg Thr Met Glu
            420                 425                 430

Ala Val Gln Gly Leu Leu Glu Gln Gly Arg Gln His Ser Gln Asp Leu
        435                 440                 445

Ala Phe Val Ser Met Leu Asn Asp Ile Ala Ala Thr Pro Thr Ala Ala
    450                 455                 460

Met Pro Phe Arg Gly Tyr Thr Val Leu Gly Val Glu Gly His Val Gln
465                 470                 475                 480

Glu Val Gln Gln Val Pro Ala Ser Gln Arg Pro Leu Trp Phe Ile Cys
                485                 490                 495

Ser Gly Met Gly Thr Gln Trp Arg Gly Met Gly Leu Ser Leu Met Arg
            500                 505                 510

Leu Asp Ser Phe Arg Glu Ser Ile Leu Arg Ser Asp Glu Ala Leu Lys
        515                 520                 525

Pro Leu Gly Val Lys Val Ser Asp Leu Leu Leu Ser Thr Asp Glu His
    530                 535                 540

Thr Phe Asp Asp Ile Val His Ser Phe Val Ser Leu Thr Ala Ile Gln
545                 550                 555                 560

Ile Ala Leu Ile Asp Leu Leu Thr Ser Met Gly Leu Lys Pro Asp Gly
                565                 570                 575

Ile Ile Gly His Ser Leu Gly Glu Val Ala Cys Gly Tyr Ala Asp Gly
            580                 585                 590

Cys Leu Ser Gln Arg Glu Ala Val Leu Ala Ala Tyr Trp Arg Gly Gln
        595                 600                 605

Cys Ile Lys Asp Ala Asn Leu Pro Ala Gly Ser Met Ala Ala Val Gly
    610                 615                 620

Leu Ser Trp Glu Glu Cys Lys Gln Arg Cys Pro Pro Gly Val Val Pro
625                 630                 635                 640

Ala Cys His Asn Ser Glu Asp Thr Val Thr Ile Ser Gly Pro Gln Ala
                645                 650                 655

Ala Val Asn Glu Phe Val Glu Gln Leu Lys Gln Glu Gly Val Phe Ala
            660                 665                 670

Lys Glu Val Arg Thr Gly Gly Leu Ala Phe His Ser Tyr Phe Met Glu
        675                 680                 685

Gly Ile Ala Pro Thr Leu Leu Gln Ala Leu Lys Lys Val Ile Arg Glu
```

690 695 700

Pro Arg Pro Arg Ser Ala Arg Trp Leu Ser Thr Ser Ile Pro Glu Ala
705 710 715 720

Gln Trp Gln Ser Ser Leu Ala Arg Thr Ser Ser Ala Glu Tyr Asn Val
725 730 735

Asn Asn Leu Val Ser Pro Val Leu Phe Gln Glu Ala Leu Trp His Val
740 745 750

Pro Glu His Ala Val Val Leu Glu Ile Ala Pro His Ala Leu Leu Gln
755 760 765

Ala Val Leu Lys Arg Gly Val Lys Pro Ser Cys Thr Ile Ile Pro Leu
770 775 780

Met Lys Arg Asp His Lys Asp Asn Leu Glu Phe Phe Leu Thr Asn Leu
785 790 795 800

Gly Lys Val His Leu Thr Gly Ile Asp Ile Asn Pro Asn Ala Leu Phe
805 810 815

Pro Pro Val Glu Phe Pro Val Pro Arg Gly Thr Pro Leu Ile Ser Pro
820 825 830

His Ile Lys Trp Asp His Ser Gln Thr Trp Asp Ile Pro Val Ala Glu
835 840 845

Asp Phe Pro Asn Gly Ser Ser Ser Ser Ser Ala Thr Val Tyr Asn Ile
850 855 860

Asp Ala Ser Ser Glu Ser Ser Asp His Tyr Leu Val Asp His Cys Ile
865 870 875 880

Asp Gly Arg Val Leu Phe Pro Gly Thr Gly Tyr Leu Tyr Leu Val Trp
885 890 895

Lys Thr Leu Ala Arg Ser Leu Ser Leu Ser Leu Glu Glu Thr Pro Val
900 905 910

Val Phe Glu Asn Val Thr Phe His Gln Ala Thr Ile Leu Pro Arg Thr
915 920 925

Gly Thr Val Pro Leu Glu Val Arg Leu Leu Glu Ala Ser His Ala Phe
930 935 940

Glu Val Ser Asp Ser Gly Asn Leu Ile Val Ser Gly Lys Val Tyr Gln
945 950 955 960

Trp Glu Asp Pro Asp Ser Lys Leu Phe Asp His Pro Glu Val Pro Ile
965 970 975

Pro Ala Glu Ser Glu Ser Val Ser Arg Leu Thr Gln Gly Glu Val Tyr
980 985 990

Lys Glu Leu Arg Leu Arg Gly Tyr Asp Tyr Gly Pro His Phe Gln Gly
995 1000 1005

Val Tyr Glu Ala Thr Leu Glu Gly Glu Gln Gly Lys Leu Leu Trp Lys
1010 1015 1020

```
Asp Asn Trp Val Thr Phe Met Asp Thr Met Leu Gln Ile Ser Ile Leu
1025                1030                1035                1040

Gly Phe Ser Lys Gln Ser Leu Gln Leu Pro Thr Arg Val Thr Ala Ile
                    1045                1050                1055

Tyr Ile Asp Pro Ala Thr His Leu Gln Lys Val Tyr Met Leu Glu Gly
            1060                1065                1070

Asp Thr Gln Val Ala Asp Val Thr Thr Ser Arg Cys Leu Gly Val Thr
        1075                1080                1085

Val Ser Gly Gly Val Tyr Ile Ser Arg Leu Gln Thr Thr Ala Thr Ser
    1090                1095                1100

Arg Arg Gln Gln Glu Gln Leu Val Pro Thr Leu Glu Lys Phe Val Phe
1105                1110                1115                1120

Thr Pro His Val Glu Pro Glu Cys Leu Ser Glu Ser Ala Ile Leu Gln
                    1125                1130                1135

Lys Glu Leu Gln Leu Cys Lys Gly Leu Ala Lys Ala Leu Gln Thr Lys
            1140                1145                1150

Ala Thr Gln Gln Gly Leu Lys Met Thr Val Pro Gly Leu Glu Asp Leu
        1155                1160                1165

Pro Gln His Gly Leu Pro Arg Leu Leu Ala Ala Ala Cys Gln Leu Gln
    1170                1175                1180

Leu Asn Gly Asn Leu Gln Leu Glu Leu Gly Glu Val Leu Ala Arg Glu
1185                1190                1195                1200

Arg Leu Leu Leu Pro Glu Asp Pro Leu Ile Ser Gly Leu Leu Asn Ser
                    1205                1210                1215

Gln Ala Leu Lys Ala Cys Ile Asp Thr Ala Leu Glu Asn Leu Ser Thr
            1220                1225                1230

Leu Lys Met Lys Val Val Glu Val Leu Ala Gly Glu Gly His Leu Tyr
        1235                1240                1245

Ser His Ile Ser Ala Leu Leu Asn Thr Gln Pro Met Leu Gln Leu Glu
    1250                1255                1260

Tyr Thr Ala Thr Asp Arg His Pro Gln Ala Leu Lys Asp Val Gln Thr
1265                1270                1275                1280

Lys Leu Gln Gln His Asp Val Ala Gln Gly Gln Trp Asp Pro Ser Gly
                    1285                1290                1295

Pro Ala Pro Thr Asn Leu Gly Ala Leu Asp Leu Val Val Cys Asn Cys
            1300                1305                1310

Ala Leu Ala Thr Leu Gly Asp Pro Ala Leu Ala Leu Asp Asn Met Val
        1315                1320                1325

Ala Ala Leu Lys Asp Gly Gly Phe Leu Leu Met His Thr Val Leu Lys
    1330                1335                1340

Gly His Ala Leu Gly Glu Thr Leu Ala Cys Leu Pro Ser Glu Val Gln
1345                1350                1355                1360
```

```
Pro Gly Pro Ser Phe Leu Ser Gln Glu Glu Trp Glu Ser Leu Phe Ser
                1365                1370                1375

Arg Lys Ala Leu His Leu Val Gly Leu Lys Lys Ser Phe Tyr Gly Thr
            1380                1385                1390

Ala Leu Phe Leu Cys Arg Arg Leu Ser Pro Gln Asp Lys Pro Ile Phe
        1395                1400                1405

Leu Pro Val Glu Asp Thr Ser Phe Gln Trp Val Asp Ser Leu Lys Ser
    1410                1415                1420

Ile Leu Ala Thr Ser Ser Ser Gln Pro Val Trp Leu Thr Ala Met Asn
1425                1430                1435                1440

Cys Pro Thr Ser Gly Val Val Gly Leu Val Asn Cys Leu Arg Lys Glu
                1445                1450                1455

Pro Gly Gly His Arg Ile Arg Cys Ile Leu Leu Ser Asn Leu Ser Ser
            1460                1465                1470

Thr Ser His Val Pro Lys Leu Asp Pro Gly Ser Ser Glu Leu Gln Lys
        1475                1480                1485

Val Leu Glu Ser Asp Leu Val Met Asn Val Tyr Arg Asp Gly Ala Trp
    1490                1495                1500

Gly Ala Phe Arg His Phe Gln Leu Glu Gln Asp Lys Pro Glu Glu Gln
1505                1510                1515                1520

Thr Ala His Ala Phe Val Asn Val Leu Thr Arg Gly Asp Leu Ala Ser
                1525                1530                1535

Ile Arg Trp Val Ser Ser Pro Leu Lys His Met Gln Pro Pro Ser Ser
            1540                1545                1550

Ser Gly Ala Gln Leu Cys Thr Val Tyr Tyr Ala Ser Leu Asn Phe Arg
        1555                1560                1565

Asp Ile Met Leu Ala Thr Gly Lys Leu Ser Pro Asp Ala Ile Pro Gly
    1570                1575                1580

Lys Trp Ala Ser Arg Asp Cys Met Leu Gly Met Glu Phe Ser Gly Arg
1585                1590                1595                1600

Asp Lys Cys Gly Arg Arg Val Met Gly Leu Val Pro Ala Glu Gly Leu
                1605                1610                1615

Ala Thr Ser Val Leu Leu Ser Pro Asp Phe Leu Trp Asp Val Pro Ser
            1620                1625                1630

Ser Trp Thr Leu Glu Glu Ala Ala Ser Val Pro Val Val Tyr Thr Thr
        1635                1640                1645

Ala Tyr Tyr Ser Leu Val Val Arg Gly Arg Ile Gln His Gly Glu Thr
    1650                1655                1660

Val Leu Ile His Ser Gly Ser Gly Gly Val Gly Gln Ala Ala Ile Ser
1665                1670                1675                1680

Ile Ala Leu Ser Leu Gly Cys Arg Val Phe Thr Thr Val Gly Ser Ala
```

```
                1685                1690                1695

Glu Lys Arg Ala Tyr Leu Gln Ala Arg Phe Pro Gln Leu Asp Asp Thr
            1700                1705                1710

Ser Phe Ala Asn Ser Arg Asp Thr Ser Phe Glu Gln His Val Leu Leu
        1715                1720                1725

His Thr Gly Gly Lys Gly Val Asp Leu Val Leu Asn Ser Leu Ala Glu
    1730                1735                1740

Glu Lys Leu Gln Ala Ser Val Arg Cys Leu Ala Gln His Gly Arg Phe
1745                1750                1755                1760

Leu Glu Ile Gly Lys Phe Asp Leu Ser Asn Asn His Pro Leu Gly Met
                1765                1770                1775

Ala Ile Phe Leu Lys Asn Val Thr Phe His Gly Ile Leu Leu Asp Ala
            1780                1785                1790

Leu Phe Glu Gly Ala Asn Asp Ser Trp Arg Glu Val Ala Glu Leu Leu
        1795                1800                1805

Lys Ala Gly Ile Arg Asp Gly Val Val Lys Pro Leu Lys Cys Thr Val
    1810                1815                1820

Phe Pro Lys Ala Gln Val Glu Asp Ala Phe Arg Tyr Met Ala Gln Gly
1825                1830                1835                1840

Lys His Ile Gly Lys Val Leu Val Gln Val Arg Glu Glu Glu Pro Glu
                1845                1850                1855

Ala Met Leu Pro Gly Ala Gln Pro Thr Leu Ile Ser Ala Ile Ser Lys
            1860                1865                1870

Thr Phe Cys Pro Glu His Lys Ser Tyr Ile Ile Thr Gly Gly Leu Gly
        1875                1880                1885

Gly Phe Gly Leu Glu Leu Ala Arg Trp Leu Val Leu Arg Gly Ala Gln
    1890                1895                1900

Arg Leu Val Leu Thr Ser Arg Ser Gly Ile Arg Thr Gly Tyr Gln Ala
1905                1910                1915                1920

Lys His Val Arg Glu Trp Arg Arg Gln Gly Ile His Val Leu Val Ser
                1925                1930                1935

Thr Ser Asn Val Ser Ser Leu Glu Gly Ala Arg Ala Leu Ile Ala Glu
            1940                1945                1950

Ala Thr Lys Leu Gly Pro Val Gly Gly Val Phe Asn Leu Ala Met Val
        1955                1960                1965

Leu Arg Asp Ala Met Leu Glu Asn Gln Thr Pro Glu Leu Phe Gln Asp
    1970                1975                1980

Val Asn Lys Pro Lys Tyr Asn Gly Thr Leu Asn Leu Asp Arg Ala Thr
1985                1990                1995                2000

Arg Glu Ala Cys Pro Glu Leu Asp Tyr Phe Val Ala Phe Ser Ser Val
                2005                2010                2015
```

Ser Cys Gly Arg Gly Asn Ala Gly Gln Ser Asn Tyr Gly Phe Ala Asn
2020 2025 2030

Ser Thr Met Glu Arg Ile Cys Glu Gln Arg Arg His Asp Gly Leu Pro
2035 2040 2045

Gly Leu Ala Val Gln Trp Gly Ala Ile Gly Asp Val Gly Ile Ile Leu
2050 2055 2060

Glu Ala Met Gly Thr Asn Asp Thr Val Val Gly Gly Thr Leu Pro Gln
2065 2070 2075 2080

Arg Ile Ser Ser Cys Met Glu Val Leu Asp Leu Phe Leu Asn Gln Pro
2085 2090 2095

His Ala Val Leu Ser Ser Phe Val Leu Ala Glu Lys Lys Ala Val Ala
2100 2105 2110

His Gly Asp Gly Glu Ala Gln Arg Asp Leu Val Lys Ala Val Ala His
2115 2120 2125

Ile Leu Gly Ile Arg Asp Leu Ala Gly Ile Asn Leu Asp Ser Ser Leu
2130 2135 2140

Ala Asp Leu Gly Leu Asp Ser Leu Met Gly Val Glu Val Arg Gln Ile
2145 2150 2155 2160

Leu Glu Arg Glu His Asp Leu Val Leu Pro Ile Arg Glu Val Arg Gln
2165 2170 2175

Leu Thr Leu Arg Lys Leu Gln Glu Met Ser Ser Lys Ala Gly Ser Asp
2180 2185 2190

Thr Glu Leu Ala Ala Pro Lys Ser Lys Asn Asp Thr Ser Leu Lys Gln
2195 2200 2205

Ala Gln Leu Asn Leu Ser Ile Leu Leu Val Asn Pro Glu Gly Pro Thr
2210 2215 2220

Leu Thr Arg Leu Asn Ser Val Gln Ser Ser Glu Arg Pro Leu Phe Leu
2225 2230 2235 2240

Val His Pro Ile Glu Gly Ser Ile Thr Val Phe His Ser Leu Ala Ala
2245 2250 2255

Lys Leu Ser Val Pro Thr Tyr Gly Leu Gln Cys Thr Gln Ala Ala Pro
2260 2265 2270

Leu Asp Ser Ile Pro Asn Leu Ala Ala Tyr Tyr Ile Asp Cys Ile Lys
2275 2280 2285

Gln Val Gln Pro Glu Gly Pro Tyr Arg Val Ala Gly Tyr Ser Phe Gly
2290 2295 2300

Ala Cys Val Ala Phe Glu Met Cys Ser Gln Leu Gln Ala Gln Gln Gly
2305 2310 2315 2320

Pro Ala Pro Ala His Asn Asn Leu Phe Leu Phe Asp Gly Ser His Thr
2325 2330 2335

Tyr Val Leu Ala Tyr Thr Gln Ser Tyr Arg Ala Lys Leu Thr Pro Gly
2340 2345 2350

```
Cys Glu Ala Glu Ala Glu Ala Glu Ala Ile Cys Phe Phe Ile Lys Gln
       2355                2360                2365

Phe Val Asp Ala Glu His Ser Lys Val Leu Glu Ala Leu Leu Pro Leu
   2370                2375                2380

Lys Ser Leu Glu Asp Arg Val Ala Ala Ala Val Asp Leu Ile Thr Arg
2385                2390                2395                2400

Ser His Gln Ser Leu Asp Arg Arg Asp Leu Ser Phe Ala Ala Val Ser
               2405                2410                2415

Phe Tyr Tyr Lys Leu Arg Ala Ala Asp Gln Tyr Lys Pro Lys Ala Lys
           2420                2425                2430

Tyr His Gly Asn Val Ile Leu Leu Arg Ala Lys Thr Gly Gly Thr Tyr
       2435                2440                2445

Gly Glu Asp Leu Gly Ala Asp Tyr Asn Leu Ser Gln Val Cys Asp Gly
   2450                2455                2460

Lys Val Ser Val His Ile Ile Glu Gly Asp His Arg Thr Leu Leu Glu
2465                2470                2475                2480

Gly Arg Gly Leu Glu Ser Ile Ile Asn Ile Ile His Ser Ser Leu Ala
               2485                2490                2495

Glu Pro Arg Val Ser Val Arg Glu Gly
           2500                2505
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<210> 21
<211> 9143
<212> DNA
<213> Rattus norvegicus

<220>
<223> Fatty acid synthase

<400> 21

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ctccagatcc cagacagaga agagccatgg aggaggtggt gatagccggt atgtccggga 120
aattgcccga gtcagagaac ctgcaggagt tctgggccaa cctcattggc ggtgtggaca 180
tggtcacaga cgatgacagg aggtggaagg ctgggctcta tgggttgcct aagcggtctg 240
gaaagctgaa ggatctgtcc aagttcgacg cctccttttt tggggtccac cccaagcagg 300
cacacacaat ggacccgcag ctccggctgc tgctggaagt cagctatgaa gctattgtgg 360
acggaggtat caacccggcc tcactccgag gaacaaacac tggtgtctgg gtgggtgtga 420
gtggttccga ggcgtcggag gccctgagca gagatcctga gactcttctg ggctacagca 480
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Ser Gln Phe Asp Glu Glu Leu Tyr Lys Val Ile Gly Lys Gly Ser Glu
                245                 250                 255

Lys Ser Asp Asp Asn Ser Tyr Asp Glu Lys Tyr Leu Ile Ala Thr Ser
            260                 265                 270

Glu Gln Pro Ile Ala Ala Leu His Arg Asp Glu Trp Leu Arg Pro Glu
        275                 280                 285

Asp Leu Pro Ile Lys Tyr Ala Gly Leu Ser Thr Cys Phe Arg Gln Glu
    290                 295                 300

Val Gly Ser His Gly Arg Asp Thr Arg Gly Ile Phe Arg Val His Gln
305                 310                 315                 320

Phe Glu Lys Ile Glu Gln Phe Val Tyr Ser Ser Pro His Asp Asn Lys
                325                 330                 335

Ser Trp Glu Met Phe Glu Glu Met Ile Thr Thr Ala Glu Glu Phe Tyr
            340                 345                 350

Gln Ser Leu Gly Ile Pro Tyr His Ile Val Asn Ile Val Ser Gly Ser
        355                 360                 365

Leu Asn His Ala Ala Ser Lys Lys Leu Asp Leu Glu Ala Trp Phe Pro
    370                 375                 380

Gly Ser Gly Ala Phe Arg Glu Leu Val Ser Cys Ser Asn Cys Thr Asp
385                 390                 395                 400

Tyr Gln Ala Arg Arg Leu Arg Ile Arg Tyr Gly Gln Thr Lys Lys Met
                405                 410                 415

Met Asp Lys Val Glu Phe Val His Met Leu Asn Ala Thr Met Cys Ala
            420                 425                 430

Thr Thr Arg Thr Ile Cys Ala Ile Leu Glu Asn Tyr Gln Thr Glu Lys
        435                 440                 445

Gly Ile Thr Val Pro Glu Lys Leu Lys Glu Phe Met Pro Pro Gly Leu
    450                 455                 460
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Gln Glu Leu Ile Pro Phe Val Lys Pro Ala Pro Ile Glu Gln Glu Pro
465 470 475 480

Ser Lys Lys Gln Lys Lys Gln His Glu Gly Ser Lys Lys Lys Ala Ala
485 490 495

Ala Arg Asp Val Thr Leu Glu Asn Arg Leu Gln Asn Met Glu Val Thr
500 505 510

Asp Ala

<210> 25
<211> 1846
<212> DNA
<213> Homo sapiens

<220>
<223> Seryl t-RNA synthetase

<400> 25
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ccagccctca tccgagagac gcaggagaag cgcttcaagg acccgggact agtggaccag 180
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<210> 26
<211> 434
<212> PRT
<213> Homo sapiens

<220>

<223> Alpha-enolase

<400> 26

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 1               5                  10                  15

Asn Pro Thr Val Glu Val Asp Leu Phe Thr Ser Lys Gly Leu Phe Arg
            20                  25                  30

Ala Ala Val Pro Ser Gly Ala Ser Thr Gly Ile Tyr Glu Ala Leu Glu
        35                  40                  45

Leu Arg Asp Asn Asp Lys Thr Arg Tyr Met Gly Lys Gly Val Ser Lys
    50                  55                  60

Ala Val Glu His Ile Asn Lys Thr Ile Ala Pro Ala Leu Val Ser Lys
65                  70                  75                  80

Lys Leu Asn Val Thr Glu Gln Glu Lys Ile Asp Lys Leu Met Ile Glu
                85                  90                  95

Met Asp Gly Thr Glu Asn Lys Ser Lys Phe Gly Ala Asn Ala Ile Leu
            100                 105                 110

Gly Val Ser Leu Ala Val Cys Lys Ala Gly Ala Val Glu Lys Gly Val
        115                 120                 125

Pro Leu Tyr Arg His Ile Ala Asp Leu Ala Gly Asn Ser Glu Val Ile
    130                 135                 140

Leu Pro Val Pro Ala Phe Asn Val Ile Asn Gly Gly Ser His Ala Gly
145                 150                 155                 160

Asn Lys Leu Ala Met Gln Glu Phe Met Ile Leu Pro Val Gly Ala Ala
                165                 170                 175

Asn Phe Arg Glu Ala Met Arg Ile Gly Ala Glu Val Tyr His Asn Leu
            180                 185                 190

Lys Asn Val Ile Lys Glu Lys Tyr Gly Lys Asp Ala Thr Asn Val Gly
        195                 200                 205

Asp Glu Gly Gly Phe Ala Pro Asn Ile Leu Glu Asn Lys Glu Gly Leu
    210                 215                 220

Glu Leu Leu Lys Thr Ala Ile Gly Lys Ala Gly Tyr Thr Asp Lys Val
225                 230                 235                 240

Val Ile Gly Met Asp Val Ala Ala Ser Glu Phe Phe Arg Ser Gly Lys
                245                 250                 255

Tyr Asp Leu Asp Phe Lys Ser Pro Asp Asp Pro Ser Arg Tyr Ile Ser
            260                 265                 270

Pro Asp Gln Leu Ala Asp Leu Tyr Lys Ser Phe Ile Lys Asp Tyr Pro
        275                 280                 285

Val Val Ser Ile Glu Asp Pro Phe Asp Gln Asp Asp Trp Gly Ala Trp
    290                 295                 300

Gln Lys Phe Thr Ala Ser Ala Gly Ile Gln Val Val Gly Asp Asp Leu
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305                 310                 315                 320

Thr Val Thr Asn Pro Lys Arg Ile Ala Lys Ala Val Asn Glu Lys Ser
                325                 330                 335

Cys Asn Cys Leu Leu Leu Lys Val Asn Gln Ile Gly Ser Val Thr Glu
            340                 345                 350

Ser Leu Gln Ala Cys Lys Leu Ala Gln Ala Asn Gly Trp Gly Val Met
        355                 360                 365

Val Ser His Arg Ser Gly Glu Thr Glu Asp Thr Phe Ile Ala Asp Leu
    370                 375                 380

Val Val Gly Leu Cys Thr Gly Gln Ile Lys Thr Gly Ala Pro Cys Arg
385                 390                 395                 400

Ser Glu Arg Leu Ala Lys Tyr Asn Gln Leu Leu Arg Ile Glu Glu Glu
                405                 410                 415

Leu Gly Ser Lys Ala Lys Phe Ala Gly Arg Asn Phe Arg Asn Pro Leu
            420                 425                 430

Ala Lys
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<210> 27
<211> 1755
<212> DNA
<213> Homo sapiens

<220>
<223> Alpha-enolase

<400> 27

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caataaaact attgcgcctg ccctggttag caagaaactg aacgtcacag aacaagagaa 360
gattgacaaa ctgatgatcg agatggatgg aacagaaaat aaatctaagt ttggtgcgaa 420
cgccattctg ggggtgtccc ttgccgtctg caaagctggt gccgttgaga agggggtccc 480
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gatcctccca gtcggtgcag caaacttcag ggaagccatg cgcattggag cagaggttta 660
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tgaaggcggg tttgctccca acatcctgga gaataaagaa ggcctggagc tgctgaagac 780
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aagtcattgt ttttctcgcc tcactttcca ccaagtgtct agagtcatgt gagcctcgtg 1680
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tcagtgaccc atgag 1755

<210> 28
<211> 316
<212> PRT
<213> Rattus norvegicus

<220>
<223> Aldose reductase

<400> 28

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Gly	Leu	Gly	Thr	Trp	Lys	Ser	Pro	Pro	Gly	Gln	Val	Thr	Glu	Ala	Val
		20					25					30			
Lys	Val	Ala	Ile	Asp	Met	Gly	Tyr	Arg	His	Ile	Asp	Cys	Ala	Gln	Val
	35					40					45				
Tyr	Gln	Asn	Glu	Lys	Glu	Val	Gly	Val	Ala	Leu	Gln	Glu	Lys	Leu	Lys
50					55					60					
Glu	Gln	Val	Val	Lys	Arg	Gln	Asp	Leu	Phe	Ile	Val	Ser	Lys	Leu	Trp
65				70					75					80	
Cys	Thr	Phe	His	Asp	Gln	Ser	Met	Val	Lys	Gly	Ala	Cys	Gln	Lys	Thr
			85					90					95		
Leu	Ser	Asp	Leu	Gln	Leu	Asp	Tyr	Leu	Asp	Leu	Tyr	Leu	Ile	His	Trp
		100					105					110			
Pro	Thr	Gly	Phe	Lys	Pro	Gly	Pro	Asp	Tyr	Phe	Pro	Leu	Asp	Ala	Ser
	115					120					125				
Gly	Asn	Val	Ile	Pro	Ser	Asp	Thr	Asp	Phe	Val	Asp	Thr	Trp	Thr	Ala
130					135					140					
Met	Glu	Gln	Leu	Val	Asp	Glu	Gly	Leu	Val	Lys	Ala	Ile	Gly	Val	Ser
145				150					155					160	
Asn	Phe	Asn	Pro	Leu	Gln	Ile	Glu	Arg	Ile	Leu	Asn	Lys	Pro	Gly	Leu
			165					170					175		
Lys	Tyr	Lys	Pro	Ala	Val	Asn	Gln	Ile	Glu	Cys	His	Pro	Tyr	Leu	Thr
		180					185					190			
Gln	Glu	Lys	Leu	Ile	Glu	Tyr	Cys	His	Cys	Lys	Gly	Ile	Val	Val	Thr
	195					200					205				
Ala	Tyr	Ser	Pro	Leu	Gly	Ser	Pro	Asp	Arg	Pro	Trp	Ala	Lys	Pro	Glu
210					215					220					
Asp	Pro	Ser	Leu	Leu	Glu	Asp	Pro	Arg	Ile	Lys	Glu	Ile	Ala	Ala	Lys
225				230					235					240	

Tyr Asn Lys Thr Thr Ala Gln Val Leu Ile Arg Phe Pro Ile Gln Arg
245 250 255

Asn Leu Val Val Ile Pro Lys Ser Val Thr Pro Ala Arg Ile Ala Glu
260 265 270

Asn Phe Lys Val Phe Asp Phe Glu Leu Ser Asn Glu Asp Met Ala Thr
275 280 285

Leu Leu Ser Tyr Asn Arg Asn Trp Arg Val Cys Ala Leu Met Ser Cys
290 295 300

Ala Lys His Lys Asp Tyr Pro Phe His Ala Glu Val
305 310 315

<210> 29
<211> 1337
<212> DNA
<213> Rattus norvegicus

<220>
<223> Aldose reductase

<400> 29
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ccgaggctgt gaaggttgct atcgacatgg ggtatcgcca cattgactgc gcccaggtgt 180
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<210> 30
<211> 299
<212> PRT
<213> Rattus norvegicus

<220>
<223> Cytochrome C oxidase, subunit 1

<400> 30
Glu Phe Pro Phe Phe Asp Pro Ala Gly Gly Gly Asp Pro Ile Leu Tyr
1 5 10 15

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Gln His Leu Phe Trp Phe Phe Gly His Pro Glu Val Tyr Ile Leu Ile
                20                  25                  30

Leu Pro Gly Phe Gly Ile Ile Ser His Val Val Thr Tyr Tyr Ser Gly
            35                  40                  45

Lys Lys Glu Pro Phe Gly Tyr Met Gly Met Val Trp Ala Met Met Ser
        50                  55                  60

Ile Gly Phe Leu Gly Phe Ile Val Trp Ala His His Met Phe Thr Val
65                  70                  75                  80

Gly Leu Asp Val Asp Thr Arg Ala Tyr Phe Thr Ser Ala Thr Met Ile
                85                  90                  95

Ile Ala Ile Pro Thr Gly Val Lys Val Phe Ser Trp Leu Ala Thr Leu
            100                 105                 110

His Gly Gly Asn Ile Lys Trp Ser Pro Ala Met Leu Trp Ala Leu Gly
        115                 120                 125

Phe Ile Phe Leu Phe Thr Val Gly Gly Leu Thr Gly Ile Val Leu Ser
    130                 135                 140

Asn Ser Ser Leu Asp Ile Val Leu His Asp Thr Tyr Tyr Val Val Ala
145                 150                 155                 160

His Phe His Tyr Val Leu Ser Met Gly Ala Val Phe Ala Ile Met Ala
                165                 170                 175

Cys Phe Val His Trp Phe Pro Leu Phe Ser Gly Tyr Thr Leu Asn Asp
            180                 185                 190

Thr Trp Ala Lys Ala His Phe Ala Ile Met Phe Val Gly Val Asn Met
        195                 200                 205

Thr Phe Phe Pro Gln His Phe Leu Gly Leu Ala Gly Met Pro Arg Arg
    210                 215                 220

Tyr Ser Asp Tyr Pro Asp Ala Tyr Thr Thr Trp Asn Thr Val Ser Ser
225                 230                 235                 240

Met Gly Ser Phe Ile Ser Leu Thr Ala Val Leu Val Met Ile Phe Met
                245                 250                 255

Ile Trp Glu Ala Phe Ala Ser Lys Arg Glu Val Leu Ser Ile Ser Tyr
            260                 265                 270

Ser Ser Thr Asn Leu Glu Trp Leu His Gly Cys Pro Pro Pro Tyr His
        275                 280                 285

Thr Phe Glu Glu Pro Ser Tyr Val Lys Val Lys
    290                 295
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<210> 31
<211> 987
<212> DNA
<213> Rattus norvegicus

<220>
<223> Cytochrome C oxidase, subunit 1

<400> 31
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catgtagtta cctattactc tggaaaaaaa gaacccttcg gatatatagg tatggtatga 180
gccataatat ctattggctt cctaggattt attgtatgag cacatcacat attcacagta 240
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<210> 32
<211> 334
<212> PRT
<213> Rattus norvegicus

<220>
<223> LDH-B

<400> 32
Met Ala Thr Leu Lys Glu Lys Leu Ile Ala Pro Val Ala Asp Asp Glu
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Thr Ala Val Pro Asn Asn Lys Ile Thr Val Val Gly Val Gly Gln Val
20 25 30

Gly Met Ala Cys Ala Ile Ser Ile Leu Gly Lys Ser Leu Ala Asp Glu
35 40 45

Leu Ala Leu Val Asp Val Leu Glu Asp Lys Leu Lys Gly Glu Met Met
50 55 60

Asp Leu Gln His Gly Ser Leu Phe Leu Gln Thr Pro Lys Ile Val Ala
65 70 75 80

Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Val Thr
85 90 95

Ala Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln
100 105 110

Arg Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr
115 120 125

Ser Pro Asp Cys Thr Ile Ile Val Val Ser Asn Pro Val Asp Ile Leu
130 135 140

Thr Tyr Val Thr Trp Lys Leu Ser Gly Leu Pro Lys His Arg Val Ile
145 150 155 160

Gly Ser Gly Cys Asn Leu Asp Ser Ala Arg Phe Arg Tyr Leu Met Ala

165 170 175

Glu Lys Leu Gly Ile His Pro Ser Ser Cys His Gly Trp Ile Leu Gly
180 185 190

Glu His Gly Asp Ser Ser Val Ala Val Trp Ser Gly Val Asn Val Ala
195 200 205

Gly Val Ser Leu Gln Glu Leu Asn Pro Glu Met Gly Thr Asp Asn Asp
210 215 220

Ser Glu Asn Trp Lys Glu Val His Lys Met Val Val Asp Ser Ala Tyr
225 230 235 240

Glu Val Ile Lys Leu Lys Gly Tyr Thr Asn Trp Ala Ile Gly Leu Ser
245 250 255

Val Ala Asp Leu Ile Glu Ser Met Leu Lys Asn Leu Ser Arg Ile His
260 265 270

Pro Val Ser Thr Met Val Lys Gly Met Tyr Gly Ile Glu Asn Glu Val
275 280 285

Phe Leu Ser Leu Pro Cys Ile Leu Asn Ala Arg Gly Leu Thr Ser Val
290 295 300

Ile Asn Gln Lys Leu Lys Asp Asp Glu Val Ala Gln Leu Arg Lys Ser
305 310 315 320

Ala Asp Thr Leu Trp Asp Ile Gln Lys Asp Leu Lys Asp Leu
325 330

<210> 33
<211> 1217
<212> DNA
<213> Rattus norvegicus

<220>
<223> LDH-B

<400> 33
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tggaatggct tgtgctatca gcattctggg gaagtctctg gctgatgagc ttgccctggt 180
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tctccagact ccgaaaatcg tggctgataa agattactcc gtgacagcca attctaagat 300
tgtggtggtg accgcgggag tccgccagca ggagggggag agtcggctca acctggtgca 360
gagaaacgtc aatgtattca agttcattat tcctcagatc gtcaagtaca gccccgactg 420
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taagatggtg gtggacagtg cctatgaagt catcaagcta aaaggctaca ccaactgggc 780
catcggccta agtgtggctg acctcatcga atccatgctg aaaaacctct ctcggattca 840
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aaagtttagc aattgca 1217

<210> 34
<211> 86
<212> PRT
<213> Homo sapiens

<220>
<223> Cytochrome C oxidase subunit VIb

<400> 34
Met Ala Glu Asp Met Glu Thr Lys Ile Lys Asn Tyr Lys Thr Ala Pro
1 5 10 15

Phe Asp Ser Arg Phe Pro Asn Gln Asn Gln Thr Arg Asn Cys Trp Gln
20 25 30

Asn Tyr Leu Asp Phe His Arg Cys Gln Lys Ala Met Thr Ala Lys Gly
35 40 45

Gly Asp Ile Ser Val Cys Glu Trp Tyr Gln Arg Val Tyr Gln Ser Leu
50 55 60

Cys Pro Thr Ser Trp Val Thr Asp Trp Asp Glu Gln Arg Ala Glu Gly
65 70 75 80

Thr Phe Pro Gly Lys Ile
85

<210> 35
<211> 439
<212> DNA
<213> Homo sapiens

<220>
<223> Cytochrome C oxidase subunit VIb

<400> 35
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agaccaaaat caagaactac aagaccgccc cttttgacag ccgcttcccc aaccagaacc 120
agactagaaa ctgctggcag aactacctgg acttccaccg ctgtcagaag gcaatgaccg 180
ctaaaggagg cgatatctct gtgtgcgaat ggtaccagcg tgtgtaccag tccctctgcc 240
ccacatcctg ggtcacagac tgggatgagc aacgggctga aggcacgttt cccgggaaga 300
tctgaactgg ctgcatctcc ctttcctctg tcctccatcc ttctcccagg atggtgaagg 360
gggacctggt acccagtgat ccccacccca ggatcctaaa tcatgactta cctgctaata 420
aaaactcatt ggaaaagtg 439

<210> 36
<211> 172
<212> PRT
<213> Homo sapiens

<220>
<223> NADH: ubiquinone oxidoreductase PGIV subunit

<400> 36
Met Pro Gly Ile Val Glu Leu Pro Thr Leu Glu Glu Leu Lys Val Asp
1 5 10 15

Glu Val Lys Ile Ser Ser Ala Val Leu Lys Ala Ala Ala His His Tyr
20 25 30

Gly Ala Gln Cys Asp Lys Pro Asn Lys Glu Phe Met Leu Cys Arg Trp
35 40 45

Glu Glu Lys Asp Pro Arg Arg Cys Leu Glu Glu Gly Lys Leu Val Asn
50 55 60

Lys Cys Ala Leu Asp Phe Phe Arg Gln Ile Lys Arg His Cys Ala Glu
65 70 75 80

Pro Phe Thr Glu Tyr Trp Thr Cys Ile Asp Tyr Thr Gly Gln Gln Leu
85 90 95

Phe Arg His Cys Arg Lys Gln Gln Ala Lys Phe Asp Glu Cys Val Leu
100 105 110

Asp Lys Leu Gly Trp Val Arg Pro Asp Leu Gly Glu Leu Ser Lys Val
115 120 125

Thr Lys Val Lys Thr Asp Arg Pro Leu Pro Glu Asn Pro Tyr His Ser
130 135 140

Arg Pro Arg Pro Asp Pro Ser Pro Glu Ile Glu Gly Asp Leu Gln Pro
145 150 155 160

Ala Thr His Gly Ser Arg Phe Tyr Phe Trp Thr Lys
165 170

<210> 37
<211> 700
<212> DNA
<213> Homo sapiens

<220>
<223> NADH: ubiquinone oxidoreductase PGIV subunit

<400> 37
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agccgtcatg ccggggatag tggagctgcc cactctagag gagctgaaag tagatgaggt 120
gaaaattagt tctgctgtgc ttaaagctgc ggcccatcac tatggagctc aatgtgataa 180
gcccaacaag gaatttatgc tctgccgctg ggaagagaaa gatccgaggc ggtgtttaga 240
ggaaggcaaa ctggtcaaca agtgtgcttt ggacttcttt aggcagataa aacgtcactg 300
tgcagagcct tttacagaat attggacttg cattgattat actggccagc agttatttcg 360
tcactgtcgc aaacagcagg caaagtttga cgagtgtgtg ctggacaaac tgggctgggt 420
gcggcctgac ctgggagaac tgtcaaaggt caccaaagtg aaaacagatc gacctttacc 480
ggagaatccc tatcactcaa gaccaagacc ggatcccagc cctgagatcg agggagatct 540
gcagcctgcc acacatggca gccgctttta tttctggacc aagtaaagat gggtccgtgg 600
cccacactcg gtcatgtgct cagacaacga ctgatgaaaa cgcccatgcg gtttgcatcg 660
actgatagtg tgttctttcc gggatcacaa acattaacaa 700

<210> 38
<211> 532
<212> PRT
<213> Mus musculus

<220>
<223> succinate dehydrogenase Fp subunit

<400> 38

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Leu Arg Ala Ala Phe Gly Leu Ser Glu Ala Gly Phe Asn Thr Ala Cys
 1               5                  10                  15

Leu Thr Lys Leu Phe Pro Thr Arg Ser His Thr Val Ala Ala Gln Gly
            20                  25                  30

Gly Ile Asn Ala Ala Leu Gly Asn Met Glu Glu Asp Asn Trp Arg Trp
        35                  40                  45

His Phe Tyr Asp Thr Val Lys Gly Ser Asp Trp Leu Gly Asp Gln Asp
    50                  55                  60

Ala Ile His Tyr Met Thr Glu Gln Ala Pro Ala Ser Val Val Glu Leu
65                  70                  75                  80

Glu Asn Tyr Gly Met Pro Phe Ser Arg Thr Glu Asp Gly Lys Ile Tyr
                85                  90                  95

Gln Arg Ala Phe Gly Gly Gln Ser Leu Lys Phe Gly Lys Gly Gly Gln
            100                 105                 110

Ala His Arg Cys Cys Cys Val Ala Asp Arg Thr Gly His Ser Leu Leu
        115                 120                 125

His Thr Leu Tyr Gly Arg Ser Leu Arg Tyr Asp Thr Ser Tyr Phe Val
    130                 135                 140

Glu Tyr Phe Ala Leu Asp Leu Leu Met Glu Asn Gly Glu Cys Arg Gly
145                 150                 155                 160

Val Ile Ala Leu Cys Ile Glu Asp Gly Ser Ile His Arg Ile Arg Ala
                165                 170                 175

Lys Asn Thr Val Ile Ala Thr Gly Gly Tyr Gly Arg Thr Tyr Phe Ser
            180                 185                 190

Cys Thr Ser Ala His Thr Ser Thr Gly Asp Gly Thr Ala Met Val Thr
        195                 200                 205

Arg Ala Gly Leu Pro Cys Gln Asp Leu Glu Phe Val Gln Phe His Pro
    210                 215                 220

Thr Gly Ile Tyr Gly Ala Gly Cys Leu Ile Thr Glu Gly Cys Arg Gly
225                 230                 235                 240

Glu Gly Gly Ile Leu Ile Asn Ser Gln Gly Glu Arg Phe Met Glu Arg
                245                 250                 255

Tyr Ala Pro Val Ala Lys Asp Leu Ala Ser Arg Asp Val Val Ser Arg
            260                 265                 270

Ser Met Thr Leu Glu Ile Arg Glu Gly Arg Gly Cys Gly Pro Glu Lys
        275                 280                 285

Asp His Val Tyr Leu Gln Leu His His Leu Pro Pro Glu Gln Leu Ala
    290                 295                 300

Thr Arg Leu Pro Gly Ile Ser Glu Thr Ala Met Ile Phe Ala Gly Val
305                 310                 315                 320
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Asp Val Thr Lys Glu Pro Ile Pro Val Leu Pro Thr Val His Tyr Asn
325 330 335

Met Gly Gly Ile Pro Thr Asn Tyr Lys Gly Gln Val Leu Lys His Val
340 345 350

Asn Gly Gln Asp Gln Ile Val Pro Gly Leu Tyr Ala Cys Gly Glu Ala
355 360 365

Ala Cys Ala Ser Val His Gly Ala Asn Arg Leu Gly Ala Asn Ser Leu
370 375 380

Leu Asp Leu Val Val Phe Gly Arg Ala Cys Ala Leu Ser Ile Ala Glu
385 390 395 400

Ser Cys Arg Pro Gly Asp Lys Val Pro Ser Ile Lys Ala Asn Ala Gly
405 410 415

Glu Glu Ser Val Met Asn Leu Asp Lys Leu Arg Phe Ala Asp Gly Ser
420 425 430

Ile Arg Thr Ser Glu Leu Arg Leu Asn Met Gln Lys Ser Met Gln Asn
435 440 445

His Ala Ala Val Phe Arg Val Gly Ser Val Leu Gln Glu Gly Cys Glu
450 455 460

Lys Ile Ser Gln Leu Tyr Gly Asp Leu Lys His Leu Lys Thr Phe Asp
465 470 475 480

Arg Gly Met Val Trp Asn Thr Asp Leu Val Glu Thr Leu Glu Leu Gln
485 490 495

Asn Leu Met Leu Cys Ala Leu Gln Thr Ile Tyr Gly Ala Glu Ala Arg
500 505 510

Lys Glu Ser Arg Gly Ala His Ala Arg Glu Asp Tyr Lys Val Arg Val
515 520 525

Asp Glu Tyr Asp
530

<210> 39
<211> 1596
<212> DNA
<213> Mus musculus

<220>
<223> succinate dehydrogenase Fp subunit

<400> 39
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atggaagagg acaactggag atggcatttc tatgacactg tgaaaggctc cgactggctg 180
ggggatcagg atgccatcca ttacatgaca gagcaagctc ctgcctctgt ggttgagcta 240
gaaaattatg gtatgccatt tagcagaact gaagatggga agatttatca gcgtgcattt 300
ggtggacaga gcctcaagtt tgggaaaggc gggcaggctc atcggtgttg ctgtgtggct 360
gatcggacag gccactcact cttacacacc ttgtatggaa gatctctgcg atatgacacc 420
agttattttg tggaatattt tgcactggat cttctgatgg aaaatgggga gtgccgtggt 480
gtcattgcac tgtgcataga agatgggtcc atacaccgaa taagagcaaa aaacactgtt 540
attgctactg ggggctacgg gcgaacctac ttcagctgta catctgccca taccagcaca 600

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gaggggggga ttctcatcaa cagtcaaggt gaaaggttca tggagagata cgcccctgtt 780
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tgcgcactgc agaccatata tggtgcagaa gctcggaagg agtcccgggg agcccatgcc 1560
agggaagatt acaaagtgcg ggtcgatgag tatgat                          1596
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<210> 40
<211> 453
<212> PRT
<213> Homo sapiens

<220>
<223> Core protein II of human mitochondrial cytochrome bc-1 complex

<400> 40

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Met Lys Leu Leu Thr Arg Ala Gly Ser Phe Ser Arg Phe Tyr Ser Leu
  1               5                  10                  15

Lys Val Ala Pro Lys Val Lys Ala Thr Ala Ala Pro Ala Gly Ala Pro
             20                  25                  30

Pro Gln Pro Gln Asp Leu Glu Phe Thr Lys Leu Pro Asn Gly Leu Val
         35                  40                  45

Ile Ala Ser Leu Glu Asn Tyr Ser Pro Val Ser Arg Ile Gly Leu Phe
     50                  55                  60

Ile Lys Ala Gly Ser Arg Tyr Glu Asp Phe Ser Asn Leu Gly Thr Thr
 65                  70                  75                  80

His Leu Leu Arg Leu Thr Ser Ser Leu Thr Thr Lys Gly Ala Ser Ser
                 85                  90                  95

Phe Lys Ile Thr Arg Gly Ile Glu Ala Val Gly Gly Lys Leu Ser Val
            100                 105                 110

Thr Ala Thr Arg Glu Asn Met Ala Tyr Thr Val Glu Cys Leu Arg Gly
        115                 120                 125

Asp Val Asp Ile Leu Met Glu Phe Leu Leu Asn Val Thr Thr Ala Pro
    130                 135                 140

Glu Phe Arg Arg Trp Glu Val Ala Asp Leu Gln Pro Gln Leu Lys Ile
145                 150                 155                 160

Asp Lys Ala Val Ala Phe Gln Asn Pro Gln Thr His Val Ile Glu Asn
                165                 170                 175
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Leu His Ala Ala Ala Tyr Gln Asn Ala Leu Ala Asn Pro Leu Tyr Cys
            180                 185                 190

Pro Asp Tyr Arg Ile Gly Lys Val Thr Ser Glu Glu Leu His Tyr Phe
        195                 200                 205

Val Gln Asn His Phe Thr Ser Ala Arg Met Ala Leu Ile Gly Leu Gly
    210                 215                 220

Val Ser His Pro Val Leu Lys Gln Val Ala Glu Gln Phe Leu Asn Met
225                 230                 235                 240

Arg Gly Gly Leu Gly Leu Ser Gly Ala Lys Ala Asn Tyr Arg Gly Gly
                245                 250                 255

Glu Ile Arg Glu Gln Asn Gly Asp Ser Leu Val His Ala Ala Phe Val
            260                 265                 270

Ala Glu Ser Ala Val Ala Gly Ser Ala Glu Ala Asn Ala Phe Ser Val
        275                 280                 285

Leu Gln His Val Leu Gly Ala Gly Pro His Val Lys Arg Gly Ser Asn
    290                 295                 300

Thr Thr Ser His Leu His Gln Ala Val Ala Lys Ala Thr Gln Gln Pro
305                 310                 315                 320

Phe Asp Val Ser Ala Phe Asn Ala Ser Tyr Ser Asp Ser Gly Leu Phe
                325                 330                 335

Gly Ile Tyr Thr Ile Ser Gln Ala Thr Ala Ala Gly Asp Val Ile Lys
            340                 345                 350

Ala Ala Tyr Asn Gln Val Lys Arg Ile Ala Gln Gly Asn Leu Ser Asn
        355                 360                 365

Thr Asp Val Gln Ala Ala Lys Asn Lys Leu Lys Ala Gly Tyr Leu Met
    370                 375                 380

Ser Val Glu Ser Ser Glu Cys Phe Leu Glu Glu Val Gly Ser Gln Ala
385                 390                 395                 400

Leu Val Ala Gly Ser Tyr Met Pro Pro Ser Thr Val Leu Gln Gln Ile
                405                 410                 415

Asp Ser Val Ala Asn Ala Asp Ile Ile Asn Ala Ala Lys Lys Phe Val
            420                 425                 430

Ser Gly Gln Lys Ser Met Ala Ala Ser Gly Asn Leu Gly His Thr Pro
        435                 440                 445

Phe Val Asp Glu Leu
    450
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<210> 41
<211> 1588
<212> DNA
<213> Homo sapiens

<220>
<223> Core protein II of human mitochondrial cytochrome bc-1 complex

<400> 41
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tactaaccag agccggctct ttctcgagat tttattccct caaagttgcc cccaaagtta 120
aagccacagc tgcgcctgca ggagcaccgc cacaacctca ggaccttgag tttaccaagt 180
taccaaatgg cttggtgatt gcttctttgg aaaactattc tcctgtatca agaattggtt 240
tgttcattaa agcaggcagt agatatgagg acttcagcaa tttaggaacc acccatttgc 300
tgcgtcttac atccagtctg acgacaaaag gagcttcatc tttcaagata acccgtggaa 360
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caccagaatt tcgtcgttgg gaagtagctg accttcagcc tcagctaaag attgacaaag 540
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caaatgcatt tagtgttctt cagcatgtcc tcggtgctgg gccacatgtc aagaggggca 960
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gacctaaagt caataaaaca ttctgttt 1588

<210> 42
<211> 358
<212> PRT
<213> Rattus norvegicus

<220>
<223> Stearoyl-CoA desaturase-2

<400> 42
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Thr Thr Ile Thr Ala Pro Pro Ser Gly Gly Gln Gln Asn Gly Gly Glu
20 25 30

Lys Phe Glu Lys Asn Pro His His Trp Gly Ala Asp Val Arg Pro Glu
35 40 45

Ile Lys Asp Asp Leu Tyr Asp Pro Ser Tyr Gln Asp Glu Glu Gly Pro
50 55 60

Pro Pro Lys Leu Glu Tyr Val Trp Arg Asn Ile Ile Leu Met Ala Leu
65 70 75 80

Leu His Ile Gly Ala Leu Tyr Gly Ile Thr Leu Val Pro Ser Cys Lys
85 90 95

Val Tyr Thr Cys Leu Phe Ala Tyr Leu Tyr Tyr Val Ile Ser Ala Leu
100 105 110

Gly Ile Thr Ala Gly Ala His Arg Leu Trp Ser His Arg Thr Tyr Lys

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          115                 120                 125

Ala Arg Leu Pro Leu Arg Leu Phe Leu Ile Ile Ala Asn Thr Met Ala
    130                 135                 140

Phe Gln Asn Asp Val Tyr Glu Trp Ala Arg Asp His Arg Ala His His
145                 150                 155                 160

Lys Phe Ser Glu Thr His Ala Asp Pro His Asn Ser Arg Arg Gly Phe
                165                 170                 175

Phe Phe Ser His Val Gly Trp Leu Leu Val Arg Lys His Pro Ala Val
            180                 185                 190

Lys Glu Lys Gly Gly Lys Leu Asp Met Ser Asp Leu Lys Ala Glu Lys
        195                 200                 205

Leu Val Met Phe Gln Arg Arg Tyr Tyr Lys Pro Gly Leu Leu Leu Met
    210                 215                 220

Cys Phe Ile Leu Pro Thr Leu Val Pro Trp Tyr Cys Trp Gly Glu Thr
225                 230                 235                 240

Phe Val Asn Ser Leu Cys Val Ser Thr Phe Leu Arg Tyr Ala Val Val
                245                 250                 255

Leu Asn Ala Thr Trp Leu Val Asn Ser Ala Ala His Leu Tyr Gly Tyr
            260                 265                 270

Arg Pro Tyr Asp Lys Asn Ile Ser Ser Arg Glu Asn Ile Leu Val Ser
        275                 280                 285

Met Gly Ala Val Gly Glu Gly Phe His Asn Tyr His His Ala Phe Pro
    290                 295                 300

Tyr Asp Tyr Ser Ala Ser Glu Tyr Arg Trp His Ile Asn Phe Thr Thr
305                 310                 315                 320

Phe Phe Ile Asp Cys Met Ala Leu Leu Gly Leu Ala Tyr Asp Arg Lys
                325                 330                 335

Arg Val Ser Lys Ala Ala Val Leu Ala Arg Ile Lys Arg Thr Gly Glu
            340                 345                 350

Glu Ser Cys Lys Ser Gly
        355
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<210> 43
<211> 5055
<212> DNA
<213> Rattus norvegicus

<220>
<223> Stearoyl-CoA desaturase-2

<400> 43
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gctgccttgg ccagccagtt tttgattttt tatctgttcc ttgatcgata caaagaacct 180
aaggacatac aggacattaa tacccaactg ccagctctgg cccagggctt gtactgtgca 240
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ggggacagca gaatggagga gagaagtttg aaaagaatcc tcaccactgg ggagcagatg 480
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ggacttacaa ggctcggctg cccctgaggc tctttctcat catcgccaac accatggcat 780
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<210> 44
<211> 605
<212> PRT
<213> Rattus norvegicus

<220>
<223> Ribophorin 1

<400> 44

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Pro Thr Pro Gly Ser Ala Ser Ser Glu Ala Pro Pro Leu Val Asn Glu
             20                  25                  30

Asp Val Lys Arg Thr Val Asp Leu Ser Ser His Leu Ala Lys Val Thr
         35                  40                  45

Ala Glu Val Val Leu Ala His Pro Gly Gly Gly Ser Thr Ala Arg Ala
     50                  55                  60

Ser Ser Phe Val Leu Ala Leu Glu Pro Glu Leu Glu Ser Arg Leu Ala
 65                  70                  75                  80

His Leu Gly Val Gln Val Lys Gly Glu Asp Glu Glu Asp Asn Asn Leu
                 85                  90                  95

Glu Val Arg Glu Thr Lys Met Lys Gly Lys Ser Gly Arg Phe Phe Thr
            100                 105                 110

Val Lys Leu Pro Val Ala Leu Asp Pro Gly Ser Lys Ile Ser Ile Val
        115                 120                 125

Val Glu Thr Val Tyr Thr His Val Leu His Pro Tyr Pro Thr Gln Ile
    130                 135                 140

Thr Gln Ser Glu Lys Gln Phe Val Val Phe Glu Gly Asn His Tyr Phe
145                 150                 155                 160

Tyr Ser Pro Tyr Pro Thr Lys Thr Gln Thr Met Arg Val Arg Leu Ala
                165                 170                 175
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Ser Arg Asn Val Glu Ser His Thr Lys Leu Gly Asn Pro Ser Arg Ser
            180                 185                 190

Glu Asp Ile Leu Asp Tyr Gly Pro Phe Lys Asp Ile Pro Ala Tyr Ser
        195                 200                 205

Gln Asp Thr Phe Lys Val His Tyr Glu Asn Asn Ser Pro Phe Leu Thr
    210                 215                 220

Ile Thr Ser Met Thr Arg Val Ile Glu Val Ser His Trp Gly Asn Ile
225                 230                 235                 240

Ala Val Glu Glu Asn Val Asp Leu Lys His Thr Gly Ala Val Leu Lys
                245                 250                 255

Gly Pro Phe Ser Arg Tyr Asp Tyr Gln Arg Gln Pro Asp Ser Gly Ile
            260                 265                 270

Ser Ser Ile Arg Ser Phe Lys Thr Ile Leu Pro Ala Ala Ala Gln Asp
        275                 280                 285

Val Tyr Tyr Arg Asp Glu Ile Gly Asn Val Ser Thr Ser His Leu Leu
    290                 295                 300

Ile Leu Asp Asp Ser Val Glu Met Glu Ile Arg Pro Arg Phe Gly Leu
305                 310                 315                 320

Phe Gly Gly Trp Lys Thr His Tyr Ile Val Gly Tyr Asn Leu Pro Ser
                325                 330                 335

Tyr Glu Tyr Leu Tyr Asn Leu Gly Asp Gln Tyr Ala Leu Lys Met Arg
            340                 345                 350

Phe Val Asp His Val Phe Asp Glu Gln Val Ile Asp Ser Leu Thr Val
        355                 360                 365

Lys Ile Ile Leu Pro Glu Gly Ala Lys Asn Ile Gln Val Asp Ser Pro
    370                 375                 380

Tyr Asp Ile Ser Arg Ala Pro Asp Glu Leu His Tyr Thr Tyr Leu Asp
385                 390                 395                 400

Thr Phe Gly Arg Pro Val Ile Val Ala Tyr Lys Lys Asn Leu Val Glu
                405                 410                 415

Gln His Ile Gln Asp Ile Val Val His Tyr Thr Phe Asn Lys Val Leu
            420                 425                 430

Met Leu Gln Glu Pro Leu Leu Val Val Ala Ala Phe Tyr Ile Leu Phe
        435                 440                 445

Phe Thr Val Ile Ile Tyr Val Arg Leu Asp Phe Ser Ile Thr Lys Asp
    450                 455                 460

Pro Ala Ala Glu Ala Arg Met Lys Val Ala Cys Ile Thr Glu Gln Val
465                 470                 475                 480

Leu Thr Leu Val Asn Lys Arg Leu Gly Leu Tyr Arg His Phe Asp Glu
                485                 490                 495

Thr Val Asn Arg Tyr Lys Gln Ser Arg Asp Ile Ser Thr Leu Asn Ser
            500                 505                 510
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Gly Lys Lys Ser Leu Glu Thr Glu His Lys Ala Val Thr Ser Glu Ile
515 520 525

Ala Val Leu Gln Ser Arg Leu Lys Thr Glu Gly Ser Asp Leu Cys Asp
530 535 540

Arg Val Ser Glu Met Gln Lys Leu Asp Ala Gln Val Lys Glu Leu Val
545 550 555 560

Leu Lys Ser Ala Val Glu Ala Glu Arg Leu Val Ala Gly Lys Leu Lys
565 570 575

Lys Asp Thr Tyr Ile Glu Asn Glu Lys Leu Ser Ser Gly Lys Arg Gln
580 585 590

Glu Leu Val Thr Lys Ile Asp His Ile Leu Asp Ala Leu
595 600 605

<210> 45
<211> 2214
<212> DNA
<213> Rattus norvegicus

<220>
<223> Ribophorin 1

<400> 45
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gcggctctac agcacgagcc agctctttcg ttctggccct ggagcccgaa ctggagtcgc 240
gacttgcaca cctaggcgtg caggtaaagg gagaagatga ggaagacaac aacctagaag 300
tacgagaaac caaaatgaag gggaaaagtg ggaggttttt caccgtcaag ctcccagttg 360
ctcttgatcc tgggtccaag atctcaatcg ttgtggaaac tgtctacacc catgtgcttc 420
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gaaatgtgga gagccatacc aagctgggga acccctcaag gtctgaggac atcctggact 600
atgggccttt taaagacatc cctgcctaca gtcaggatac tttcaaagta cattatgaga 660
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tgcatggttt tttaaaagtg tgtatgacca aataaaaata aaggagggac tgtg 2214

<210> 46
<211> 284
<212> PRT
<213> Rattus norvegicus

<220>
<223> Sulfotransferase-like protein

<400> 46

Met Ala Glu Ser Glu Ala Glu Thr Pro Gly Thr Pro Gly Glu Phe Glu
1 5 10 15

Ser Lys Tyr Phe Glu Phe His Gly Val Arg Leu Pro Pro Phe Cys Arg
20 25 30

Gly Lys Met Glu Asp Ile Ala Asp Phe Pro Val Arg Pro Ser Asp Val
35 40 45

Trp Ile Val Thr Tyr Pro Lys Ser Gly Thr Ser Leu Leu Gln Glu Val
50 55 60

Val Tyr Leu Val Ser Gln Gly Ala Asp Pro Asp Glu Ile Gly Leu Met
65 70 75 80

Asn Ile Asp Glu Gln Leu Pro Val Leu Glu Tyr Pro Gln Pro Gly Leu
85 90 95

Asp Ile Ile Lys Glu Leu Thr Ser Pro Arg Leu Ile Lys Ser His Leu
100 105 110

Pro Tyr Arg Phe Leu Pro Ser Asp Leu His Asn Gly Asp Ser Lys Val
115 120 125

Ile Tyr Met Ala Arg Asn Pro Lys Asp Leu Val Val Ser Tyr Tyr Gln
130 135 140

Phe His Arg Ser Leu Arg Thr Met Ser Tyr Arg Gly Thr Phe Gln Glu
145 150 155 160

Phe Cys Arg Arg Phe Met Asn Asp Lys Leu Gly Tyr Gly Ser Trp Phe
165 170 175

Glu His Val Gln Glu Phe Trp Glu His Arg Met Asp Ala Asn Val Leu
180 185 190

Phe Leu Lys Tyr Glu Asp Met His Arg Asp Leu Val Thr Met Val Glu
195 200 205

Gln Leu Ala Arg Phe Leu Gly Val Ser Cys Asp Lys Ala Gln Leu Glu
210 215 220

Ser Leu Ile Glu His Cys His Gln Leu Val Asp Gln Cys Cys Asn Ala
225 230 235 240

Glu Ala Leu Pro Val Gly Arg Gly Arg Val Gly Leu Trp Lys Asp Ile
245 250 255

Phe Thr Val Ser Met Asn Glu Lys Phe Asp Leu Val Tyr Lys Gln Lys
260 265 270

Met Gly Lys Cys Asp Leu Thr Phe Asp Phe Tyr Leu
275 280

<210> 47
<211> 2239
<212> DNA
<213> Rattus norvegicus

<220>
<223> Sulfotransferase-like protein

<400> 47
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gcctcccttc tgccgcggga agatggagga catcgccgac ttcccagtgc ggcccagcga 180
tgtgtggatc gtcacctacc ccaagtcagg tacgagcttg ctgcaagagg cggtctactt 240
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tggaaccaca cacggtactc tgtgcttgct tgcatcttta ataaaagaca cctcccctgt 2220
caaaaaaaaa aaaaaaaaa 2239

<210> 48
<211> 235
<212> PRT
<213> Rattus norvegicus

<220>
<223> F1-ATPase alpha subunit

<400> 48
Val Ala Asp Arg Gln Met Ser Leu Leu Leu Arg Arg Pro Pro Gly Arg
1 5 10 15

Glu Ala Tyr Pro Gly Asp Val Phe Tyr Leu His Ser Arg Leu Leu Glu
20 25 30

Arg Ala Ala Lys Met Asn Asp Ser Phe Gly Gly Gly Ser Leu Thr Ala
35 40 45

Leu Pro Val Ile Glu Thr Gln Ala Gly Asp Val Ser Ala Tyr Ile Pro
50 55 60

Thr Asn Val Ile Ser Ile Thr Asp Gly Gln Ile Phe Leu Glu Thr Glu
65 70 75 80

Leu Phe Tyr Lys Gly Ile Arg Pro Ala Ile Asn Val Gly Leu Ser Val
85 90 95

Ser Arg Val Gly Ser Ala Ala Gln Thr Arg Ala Met Lys Gln Val Ala
100 105 110

Gly Thr Met Lys Leu Glu Leu Ala Gln Tyr Arg Glu Val Ala Ala Phe
115 120 125

Ala Gln Phe Gly Ser Asp Leu Asp Ala Ala Thr Gln Gln Leu Leu Ser
130 135 140

Arg Gly Val Arg Leu Thr Glu Leu Leu Lys Gln Gly Gln Tyr Ser Pro
145 150 155 160

Met Ala Ile Glu Glu Gln Val Ala Val Ile Tyr Ala Gly Val Arg Gly
165 170 175

Tyr Leu Asp Lys Leu Glu Pro Ser Lys Ile Thr Lys Phe Glu Ser Ala
180 185 190

Phe Leu Ser His Val Val Ser Gln His Gln Ser Leu Leu Gly Asn Ile
195 200 205

Arg Ser Asp Gly Lys Ile Ser Glu Gln Ser Asp Ala Lys Leu Lys Glu
210 215 220

Ile Val Thr Asn Phe Leu Ala Gly Phe Glu Pro
225 230 235

<210> 49
<211> 1066
<212> DNA
<213> Rattus norvegicus

<220>
<223> F1-ATPase alpha subunit

<400> 49
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ggtgatgtgt tttacctaca ctctcgcctg ctggagagag cagccaagat gaacgattcc 120
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gcctacattc caacaaacgt tatttccatc accgatggac agatcttctt ggaaacagaa 240
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tctgccgccc agaccagagc catgaagcag gtggcaggca ccatgaagct ggagttggcc 360
cagtaccggg aggtcgctgc ttttgcccag tttggttctg atctggatgc tgccactcag 420
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caccagagcc tcttgggcaa tatcaggtct gatgggaaaa tctcagaaca gtcggatgca 660
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gacttcaggg gttggggatt tagctcagtg gtagagcgct tgcctaggaa gcgcaaggcc 1020
ctgggttcgg tccccagctc cggaaaaaaa agaaccaacc cgaatt 1066

<210> 50
<211> 168
<212> PRT
<213> Rattus norvegicus

<220>
<223> F1F0 ATPase delta subunit

<400> 50
Met Leu Pro Ala Ala Leu Leu Arg His Pro Gly Leu Arg Arg Leu Val
1 5 10 15

Leu Gln Ala Arg Thr Tyr Ala Gln Ala Ala Ala Ser Pro Ala Pro Ala
20 25 30

Ala Gly Pro Gly Gln Met Ser Phe Thr Phe Ala Ser Pro Thr Gln Val
35 40 45

Phe Phe Asp Gly Ala Asn Val Arg Gln Val Asp Val Pro Thr Leu Thr
50 55 60

Gly Ala Phe Gly Ile Leu Ala Ser His Val Pro Thr Leu Gln Val Leu
65 70 75 80

Arg Pro Gly Leu Val Met Val His Ala Glu Asp Gly Thr Thr Thr Lys
85 90 95

Tyr Phe Val Ser Ser Gly Ser Val Thr Val Asn Ala Asp Ser Ser Val
100 105 110

Gln Leu Leu Ala Glu Glu Val Val Thr Leu Asp Met Leu Asp Leu Gly
115 120 125

Ala Ala Arg Ala Asn Leu Glu Lys Ala Gln Ser Glu Leu Ser Gly Ala
130 135 140

Ala Asp Glu Ala Ala Arg Ala Glu Ile Gln Ile Arg Ile Glu Ala Asn
145 150 155 160

Glu Ala Leu Val Lys Ala Leu Glu
165

<210> 51
<211> 811

<212> DNA
<213> Rattus norvegicus

<220>
<223> F1F0 ATPase delta subunit

<400> 51
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ggccgccgcc tcacctgccc ccgccgctgg gcctggacag atgtccttca ccttcgcctc 180
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cactgtgaat gcggactcct ctgtgcaatt actagctgaa gaagtcgtga cactggacat 420
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agcctatctg cattaaatac cacggaattc c 811

<210> 52
<211> 572
<212> PRT
<213> Homo sapiens

<220>
<223> Dihydropyrimidinase-related protein

<400> 52
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1 5 10 15

Leu Leu Ile Lys Gly Gly Lys Ile Val Asn Asp Asp Gln Ser Phe Tyr
20 25 30

Ala Asp Ile Tyr Met Glu Asp Gly Leu Ile Lys Gln Ile Gly Glu Asn
35 40 45

Leu Ile Val Pro Gly Gly Val Lys Thr Ile Glu Ala His Ser Arg Met
50 55 60

Val Ile Pro Gly Gly Ile Asp Val His Thr Arg Phe Gln Met Pro Asp
65 70 75 80

Gln Gly Met Thr Ser Ala Asp Asp Phe Phe Gln Gly Thr Lys Ala Ala
85 90 95

Leu Ala Gly Gly Thr Thr Met Ile Ile Asp His Val Val Pro Glu Pro
100 105 110

Gly Thr Ser Leu Leu Ala Ala Phe Asp Gln Trp Arg Glu Trp Ala Asp
115 120 125

Ser Lys Ser Cys Cys Asp Tyr Ser Leu His Val Asp Ile Ser Glu Trp
130 135 140

His Lys Gly Ile Gln Glu Glu Met Glu Ala Leu Val Lys Asp His Gly
145 150 155 160

Val Asn Ser Phe Leu Val Tyr Met Ala Phe Lys Asp Arg Phe Gln Leu
165 170 175

Thr Asp Cys Gln Ile Tyr Glu Val Leu Ser Val Ile Arg Asp Ile Gly
180 185 190

Ala Ile Ala Gln Val His Ala Glu Asn Gly Asp Ile Ile Ala Glu Glu
195 200 205

Gln Gln Arg Ile Leu Asp Leu Gly Ile Thr Gly Pro Glu Gly His Val
210 215 220

Leu Ser Arg Pro Glu Glu Val Glu Ala Glu Ala Val Asn Arg Ala Ile
225 230 235 240

Thr Ile Ala Asn Gln Thr Asn Cys Pro Leu Tyr Ile Thr Lys Val Met
245 250 255

Ser Lys Ser Ser Ala Glu Val Ile Ala Gln Ala Arg Lys Lys Gly Thr
260 265 270

Val Val Tyr Gly Glu Pro Ile Thr Ala Ser Leu Gly Thr Asp Gly Ser
275 280 285

His Tyr Trp Ser Lys Asn Trp Ala Lys Ala Ala Ala Phe Val Thr Ser
290 295 300

Pro Pro Leu Ser Pro Asp Pro Thr Thr Pro Asp Phe Leu Asn Ser Leu
305 310 315 320

Leu Ser Cys Gly Asp Leu Gln Val Thr Gly Ser Ala His Cys Thr Phe
325 330 335

Asn Thr Ala Gln Lys Ala Val Gly Lys Asp Asn Phe Thr Leu Ile Pro
340 345 350

Glu Gly Thr Asn Gly Thr Glu Glu Arg Met Ser Val Ile Trp Asp Lys
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Ala Val Val Thr Gly Lys Met Asp Glu Asn Gln Phe Val Ala Val Thr
370 375 380

Ser Thr Asn Ala Ala Lys Val Phe Asn Leu Tyr Pro Arg Lys Gly Arg
385 390 395 400

Ile Ala Val Gly Ser Asp Ala Asp Leu Val Ile Trp Asp Pro Asp Ser
405 410 415

Val Lys Thr Ile Ser Ala Lys Thr His Asn Ser Ser Leu Glu Tyr Asn
420 425 430

Ile Phe Glu Gly Met Glu Cys Arg Gly Ser Pro Leu Val Val Ile Ser
435 440 445

Gln Gly Lys Ile Val Leu Glu Asp Gly Thr Leu His Val Thr Glu Gly
450 455 460

Ser Gly Arg Tyr Ile Pro Arg Lys Pro Phe Pro Asp Phe Val Tyr Lys
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Arg Ile Lys Ala Arg Ser Arg Leu Ala Glu Leu Arg Gly Val Pro Arg
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Gly Leu Tyr Asp Gly Pro Val Cys Glu Val Ser Val Thr Pro Lys Thr
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Val Thr Pro Ala Ser Ser Ala Lys Thr Ser Pro Ala Lys Gln Gln Ala
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<213> Rattus norvegicus

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<223> Myelin basic protein S

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<211> 698
<212> PRT
<213> Rattus norvegicus

<220>
<223> Transferrin

<400> 55

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His Glu Asn Thr Lys Cys Ile Ser Phe Arg Asp His Met Lys Thr Val
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Leu Pro Ala Asp Gly Pro Arg Leu Ala Cys Val Lys Lys Thr Ser Tyr
    50                  55                  60

Gln Asp Cys Ile Lys Ala Ile Ser Gly Gly Glu Ala Asp Ala Ile Thr
65                  70                  75                  80

Leu Asp Gly Gly Trp Val Tyr Asp Ala Gly Leu Thr Pro Asn Asn Leu
                85                  90                  95

Lys Pro Val Ala Ala Glu Phe Tyr Gly Ser Leu Glu His Pro Gln Thr
            100                 105                 110

His Tyr Leu Ala Val Ala Val Val Lys Lys Gly Thr Asp Phe Gln Leu
        115                 120                 125

Asn Gln Leu Gln Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser
    130                 135                 140

Ala Gly Trp Ile Ile Pro Ile Gly Leu Leu Phe Cys Asn Leu Pro Glu
145                 150                 155                 160

Pro Arg Lys Pro Leu Glu Lys Ala Val Ala Ser Phe Phe Ser Gly Ser
                165                 170                 175

Cys Val Pro Cys Ala Asp Pro Val Ala Phe Pro Gln Leu Cys Gln Leu
            180                 185                 190

Cys Pro Gly Cys Gly Cys Ser Pro Thr Gln Pro Phe Phe Gly Tyr Val
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Gly Ala Phe Lys Cys Leu Arg Asp Gly Gly Gly Asp Val Ala Phe Val
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Lys His Thr Thr Ile Phe Glu Val Leu Pro Gln Lys Ala Asp Arg Asp
225                 230                 235                 240

Gln Tyr Glu Leu Leu Cys Leu Asp Asn Thr Arg Lys Pro Val Asp Gln
                245                 250                 255

Tyr Glu Asp Cys Tyr Leu Ala Arg Ile Pro Ser His Ala Val Val Ala
            260                 265                 270

Arg Asn Gly Asp Gly Lys Glu Asp Leu Ile Trp Glu Ile Leu Lys Val
        275                 280                 285

Ala Gln Glu His Phe Gly Lys Gly Lys Ser Lys Asp Phe Gln Leu Phe
    290                 295                 300

Gly Ser Pro Leu Gly Lys Asp Leu Leu Phe Lys Asp Ser Ala Phe Gly
305                 310                 315                 320

Cys Tyr Gly Val Pro Pro Arg Met Asp Tyr Arg Leu Tyr Leu Gly His
                325                 330                 335

Ser Tyr Val Thr Ala Ile Arg Asn Gln Arg Glu Gly Val Cys Pro Glu
            340                 345                 350

Ala Ser Ile Asp Ser Ala Pro Val Lys Trp Cys Ala Leu Ser His Gln
        355                 360                 365

Glu Arg Ala Lys Cys Asp Glu Trp Ser Val Thr Ser Asn Gly Gln Ile
    370                 375                 380

Glu Cys Glu Ser Ala Glu Ser Thr Glu Asp Cys Ile Asp Lys Ile Val
385                 390                 395                 400

Asn Gly Glu Ala Asp Ala Met Ser Leu Asp Gly Gly His Ala Tyr Ile
                405                 410                 415

Ala Gly Gln Cys Gly Leu Val Pro Val Met Ala Glu Asn Tyr Asp Ile
            420                 425                 430

Ser Ser Cys Thr Asn Pro Gln Ser Asp Val Phe Pro Lys Gly Tyr Tyr
        435                 440                 445

Ala Val Ala Val Val Lys Ala Ser Asp Ser Ser Ile Asn Trp Asn Asn
    450                 455                 460

Leu Lys Gly Lys Lys Ser Cys His Thr Gly Val Asp Arg Thr Ala Gly
465                 470                 475                 480

Trp Asn Ile Pro Met Gly Leu Leu Phe Ser Arg Ile Asn His Cys Lys
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Phe Asp Glu Phe Phe Ser Gln Gly Cys Ala Pro Gly Tyr Lys Lys Asn
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Ser Thr Leu Cys Asp Leu Cys Ile Gly Pro Ala Lys Cys Ala Pro Asn
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Asn Arg Glu Gly Tyr Asn Gly Tyr Thr Gly Ala Phe Gln Cys Leu Val
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Glu Lys Gly Asp Val Ala Phe Val Lys His Gln Thr Val Leu Glu Asn
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Thr Asn Gly Lys Asn Thr Ala Ala Trp Ala Lys Asp Leu Lys Gln Glu
                565                 570                 575

Asp Phe Gln Leu Leu Cys Pro Asp Gly Thr Lys Lys Pro Val Thr Glu
            580                 585                 590

Phe Ala Thr Cys His Leu Ala Gln Ala Pro Asn His Val Val Val Ser
        595                 600                 605

Arg Lys Glu Lys Ala Ala Arg Val Ser Thr Val Leu Thr Ala Gln Lys
    610                 615                 620

Asp Leu Phe Trp Lys Gly Asp Lys Asp Cys Thr Gly Asn Phe Cys Leu
625                 630                 635                 640

Phe Arg Ser Ser Thr Lys Asp Leu Leu Phe Arg Asp Asp Thr Lys Cys
                645                 650                 655

Leu Thr Lys Leu Pro Glu Gly Thr Thr Tyr Glu Glu Tyr Leu Gly Ala
            660                 665                 670

Glu Tyr Leu Gln Ala Val Gly Asn Ile Arg Lys Cys Ser Thr Ser Arg
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Leu Leu Glu Ala Cys Thr Phe His Lys Ser
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<210> 56
<211> 2293
<212> DNA
<213> Rattus norvegicus

<220>
<223> Transferrin

<400> 56

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<212> PRT
<213> Rattus norvegicus

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<223> NF-L

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             20                  25                  30

Tyr Ser Thr Ala Arg Ser Ala Tyr Ser Ser Tyr Ser Ala Pro Val Ser
         35                  40                  45

Ser Ser Leu Ser Val Arg Arg Ser Tyr Ser Ser Ser Ser Gly Ser Leu
     50                  55                  60

Met Pro Ser Leu Glu Asn Leu Asp Leu Ser Gln Val Ala Ala Ile Ser
 65                  70                  75                  80

Asn Asp Leu Lys Ser Ile Arg Thr Gln Glu Lys Ala Gln Leu Gln Asp
                 85                  90                  95

Leu Asn Asp Arg Phe Ala Ser Phe Ile Glu Arg Val His Glu Leu Glu
            100                 105                 110

Gln Gln Asn Lys Val Leu Glu Ala Glu Leu Leu Val Leu Arg Gln Lys
        115                 120                 125

His Ser Glu Pro Ser Arg Phe Arg Ala Leu Tyr Glu Gln Glu Ile Arg
    130                 135                 140

Asp Leu Arg Leu Ala Ala Glu Asp Ala Thr Asn Glu Lys Gln Ala Leu
145                 150                 155                 160

Gln Gly Glu Arg Glu Gly Leu Glu Glu Thr Leu Arg Asn Leu Gln Ala
                165                 170                 175
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Arg Tyr Glu Glu Glu Val Leu Ser Arg Glu Asp Ala Glu Gly Arg Leu
            180                 185                 190

Met Glu Ala Arg Lys Gly Ala Asp Glu Ala Ala Leu Ala Arg Ala Glu
        195                 200                 205

Leu Glu Lys Arg Ile Asp Ser Leu Met Asp Glu Ile Ala Phe Leu Lys
    210                 215                 220

Lys Val His Glu Glu Glu Ile Ala Glu Leu Gln Ala Gln Ile Gln Tyr
225                 230                 235                 240

Ala Gln Ile Ser Val Glu Met Asp Val Ser Ser Lys Pro Asp Leu Ser
                245                 250                 255

Ala Ala Leu Lys Asp Ile Arg Ala Gln Tyr Glu Lys Leu Ala Ala Lys
            260                 265                 270

Asn Met Gln Asn Ala Glu Glu Trp Phe Lys Ser Arg Phe Thr Val Leu
        275                 280                 285

Thr Glu Ser Ala Ala Lys Asn Thr Asp Ala Val Arg Ala Ala Lys Asp
    290                 295                 300

Glu Val Ser Glu Ser Arg Arg Leu Leu Lys Ala Lys Thr Leu Glu Ile
305                 310                 315                 320

Glu Ala Cys Arg Gly Met Asn Glu Ala Leu Glu Lys Gln Leu Gln Glu
                325                 330                 335

Leu Glu Asp Lys Gln Asn Ala Asp Ile Ser Ala Met Gln Asp Thr Ile
            340                 345                 350

Asn Lys Leu Glu Asn Glu Leu Arg Ser Thr Lys Ser Glu Met Ala Arg
        355                 360                 365

Tyr Leu Lys Glu Tyr Gln Asp Leu Leu Asn Val Lys Met Ala Leu Asp
    370                 375                 380

Ile Glu Ile Ala Ala Tyr Arg Lys Leu Leu Glu Gly Glu Glu Thr Arg
385                 390                 395                 400

Leu Ser Phe Thr Ser Val Gly Ser Ile Thr Ser Gly Tyr Ser Gln Ser
                405                 410                 415

Ser Gln Val Phe Gly Arg Ser Ala Tyr Ser Gly Leu Gln Ser Ser Ser
            420                 425                 430

Tyr Leu Met Ser Ala Arg Ala Phe Pro Ala Tyr Tyr Thr Ser His Val
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Gln Glu Glu Gln Ser Glu Val Glu Glu Thr Ile Glu Ala Thr Lys Ala
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Glu Glu Ala Lys Asp Glu Pro Pro Ser Glu Gly Glu Ala Glu Glu Glu
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Glu Lys Glu Lys Glu Glu Gly Glu Glu Glu Glu Gly Ala Glu Glu Glu
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Glu Ala Ala Lys Asp Glu Ser Glu Asp Ala Lys Glu Glu Glu Gly Gly
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<223> NF-L

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<213> Rattus norvegicus

<220>
<223> MAG

<400> 59

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            20                  25                  30

Phe Glu Gly Thr Cys Val Ser Ile Pro Cys Arg Phe Asp Phe Pro Asp
        35                  40                  45

Glu Leu Arg Pro Ala Val Val His Gly Val Trp Tyr Phe Asn Ser Pro
    50                  55                  60

Tyr Pro Lys Asn Tyr Pro Pro Val Val Phe Lys Ser Arg Thr Gln Val
65                  70                  75                  80

Val His Glu Ser Phe Gln Gly Arg Ser Arg Leu Leu Gly Asp Leu Gly
                85                  90                  95

Leu Arg Asn Cys Thr Leu Leu Leu Ser Thr Leu Ser Pro Glu Leu Gly
            100                 105                 110

Gly Lys Tyr Tyr Phe Arg Gly Asp Leu Gly Gly Tyr Asn Gln Tyr Thr
        115                 120                 125

Phe Ser Glu His Ser Val Leu Asp Ile Ile Asn Thr Pro Asn Ile Val
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Val Pro Pro Glu Val Val Ala Gly Thr Glu Val Glu Val Ser Cys Met
145                 150                 155                 160

Val Pro Asp Asn Cys Pro Glu Leu Arg Pro Glu Leu Ser Trp Leu Gly
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His Glu Gly Leu Gly Glu Pro Thr Val Leu Gly Arg Leu Arg Glu Asp
            180                 185                 190

Glu Gly Thr Trp Val Gln Val Ser Leu Leu His Phe Val Pro Thr Arg
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Glu Ala Asn Gly His Arg Leu Gly Cys Gln Ala Ala Phe Pro Asn Thr
    210                 215                 220

Thr Leu Gln Phe Glu Gly Tyr Ala Ser Leu Asp Val Lys Tyr Pro Pro
225                 230                 235                 240

Val Ile Val Glu Met Asn Ser Ser Val Glu Ala Ile Glu Gly Ser His
                245                 250                 255

Val Ser Leu Leu Cys Gly Ala Asp Ser Asn Pro Pro Pro Leu Leu Thr
            260                 265                 270

Trp Met Arg Asp Gly Met Val Leu Arg Glu Ala Val Ala Glu Ser Leu
        275                 280                 285

Tyr Leu Asp Leu Glu Glu Val Thr Pro Ala Glu Asp Gly Ile Tyr Ala
    290                 295                 300

Cys Leu Ala Glu Asn Ala Tyr Gly Gln Asp Asn Arg Thr Val Glu Leu
305                 310                 315                 320

Ser Val Met Tyr Ala Pro Trp Lys Pro Thr Val Asn Gly Thr Val Val
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325 330 335

Ala Val Glu Gly Glu Thr Val Ser Ile Leu Cys Ser Thr Gln Ser Asn
340 345 350

Pro Asp Pro Ile Leu Thr Ile Phe Lys Glu Lys Gln Ile Leu Ala Thr
355 360 365

Val Ile Tyr Glu Ser Gln Leu Gln Leu Glu Leu Pro Ala Val Thr Pro
370 375 380

Glu Asp Asp Gly Glu Tyr Trp Cys Val Ala Glu Asn Gln Tyr Gly Gln
385 390 395 400

Arg Ala Thr Ala Phe Asn Leu Ser Val Glu Phe Ala Pro Ile Ile Leu
405 410 415

Leu Glu Ser His Cys Ala Ala Ala Arg Asp Thr Val Gln Cys Leu Cys
420 425 430

Val Val Lys Ser Asn Pro Glu Pro Ser Val Ala Phe Glu Leu Pro Ser
435 440 445

Arg Asn Val Thr Val Asn Glu Thr Glu Arg Glu Phe Val Tyr Ser Glu
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Arg Ser Gly Leu Leu Leu Thr Ser Ile Leu Thr Leu Arg Gly Gln Ala
465 470 475 480

Gln Ala Pro Pro Arg Val Ile Cys Thr Ser Arg Asn Leu Tyr Gly Thr
485 490 495

Gln Ser Leu Glu Leu Pro Phe Gln Gly Ala His Arg Leu Met Trp Ala
500 505 510

Lys Ile Gly Pro Val Gly Ala Val Val Ala Phe Ala Ile Leu Ile Ala
515 520 525

Ile Val Cys Tyr Ile Thr Gln Thr Arg Arg Lys Lys Asn Val Thr Glu
530 535 540

Ser Pro Ser Phe Ser Ala Gly Asp Asn Pro His Val Leu Tyr Ser Pro
545 550 555 560

Glu Phe Arg Ile Ser Gly Ala Pro Asp Lys Tyr Glu Ser Glu Lys Arg
565 570 575

Leu Gly Ser Glu Arg Arg Leu Leu Gly Leu Arg Gly Glu Pro Pro Glu
580 585 590

Leu Asp Leu Ser Tyr Ser His Ser Asp Leu Gly Lys Arg Pro Thr Lys
595 600 605

Asp Ser Tyr Thr Leu Thr Glu Glu Leu Ala Glu Tyr Ala Glu Ile Arg
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Val Lys
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Ser Ser Gly Phe Arg Ser Gln Ser Trp Ser Arg Gly Ser Pro Ser Thr
            35                  40                  45

Val Ser Ser Ser Tyr Lys Arg Ser Ala Leu Ala Pro Arg Leu Ala Tyr
        50                  55                  60

Ser Ser Ala Met Leu Ser Ser Ala Glu Ser Ser Leu Asp Phe Ser Gln
65                  70                  75                  80

Ser Ser Ser Leu Leu Asn Gly Gly Ser Gly Gly Asp Tyr Lys Leu Ser
                85                  90                  95

Arg Ser Asn Glu Lys Glu Gln Leu Gln Gly Leu Asn Asp Arg Phe Ala
            100                 105                 110

Gly Tyr Ile Glu Lys Val His Tyr Leu Glu Gln Gln Asn Lys Glu Ile
        115                 120                 125

Glu Ala Glu Ile His Ala Leu Arg Gln Lys Gln Ala Ser His Ala Gln
    130                 135                 140

Leu Gly Asp Ala Tyr Asp Gln Glu Ile Arg Glu Leu Arg Ala Thr Leu
145                 150                 155                 160

Glu Met Val Asn His Glu Lys Ala Gln Val Gln Leu Asp Ser Asp His
                165                 170                 175

Leu Glu Glu Asp Ile His Arg Leu Lys Glu Arg Phe Glu Glu Glu Ala
            180                 185                 190

Arg Leu Arg Asp Asp Thr Glu Ala Ala Ile Arg Ala Val Arg Lys Asp
        195                 200                 205

Ile Glu Glu Ser Ser Met Val Lys Val Glu Leu Asp Lys Lys Val Gln
    210                 215                 220

Ser Leu Gln Asp Glu Val Ala Phe Leu Arg Ser Asn His Glu Glu Glu
225                 230                 235                 240

Val Ala Asp Leu Leu Ala Gln Ile Gln Ala Ser His Ile Thr Val Glu
                245                 250                 255

Arg Lys Asp Tyr Leu Lys Thr Asp Ile Ser Thr Ala Leu Lys Glu Ile
            260                 265                 270

Arg Ser Gln Leu Glu Cys His Ser Asp Gln Asn Met His Gln Ala Glu
        275                 280                 285

Glu Trp Phe Lys Cys Arg Tyr Ala Lys Leu Thr Glu Ala Ala Glu Gln
    290                 295                 300

Asn Lys Glu Ala Ile Arg Ser Ala Lys Glu Glu Ile Ala Glu Tyr Arg
305                 310                 315                 320

Arg Gln Leu Gln Ser Lys Ser Ile Glu Leu Glu Ser Val Arg Gly Thr
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Lys Glu Ser Leu Glu Arg Gln Leu Ser Asp Ile Glu Glu Arg His Asn
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340 345 350

His Asp Leu Ser Ser Tyr Gln Asp Thr Ile Gln Gln Leu Glu Asn Glu
355 360 365

Leu Arg Gly Thr Lys Trp Glu Met Ala Arg His Leu Arg Glu Tyr Gln
370 375 380

Asp Leu Leu Asn Val Lys Met Ala Leu Asp Ile Glu Ile Ala Ala Tyr
385 390 395 400

Arg Lys Leu Leu Glu Gly Glu Glu Thr Arg Phe Ser Thr Phe Ser Gly
405 410 415

Ser Ile Thr Gly Pro Leu Tyr Thr His Arg Gln Pro Ser Val Thr Ile
420 425 430

Ser Ser Lys Ile Gln Lys Thr Lys Val Glu Ala Pro Lys Leu Lys Val
435 440 445

Gln His Lys Phe Val Glu Glu Ile Ile Glu Glu Thr Lys Val Glu Asp
450 455 460

Glu Lys Ser Glu Met Glu Asp Ala Leu Thr Val Ile Ala Glu Glu Leu
465 470 475 480

Ala Ala Ser Ala Lys Glu Glu Lys Glu Glu Ala Glu Glu Lys Glu Glu
485 490 495

Glu Pro Glu Val Lys Ser Pro Val Lys Ser Pro Glu Ala Lys Glu Glu
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Glu Glu Gly Glu Lys Glu Glu Glu Glu Glu Gly Gln Glu Glu Glu Glu
515 520 525

Glu Glu Asp Glu Gly Val Lys Ser Asp Gln Ala Glu Glu Gly Gly Ser
530 535 540

Glu Lys Glu Gly Ser Ser Glu Lys Asp Glu Gly Glu Gln Glu Glu Glu
545 550 555 560

Gly Glu Thr Glu Ala Glu Gly Glu Gly Glu Glu Ala Glu Ala Lys Glu
565 570 575

Glu Lys Lys Thr Glu Gly Lys Val Glu Glu Met Ala Ile Lys Glu Glu
580 585 590

Ile Lys Val Glu Lys Pro Glu Lys Ala Lys Ser Pro Val Pro Lys Ser
595 600 605

Pro Val Glu Glu Val Lys Pro Lys Pro Glu Ala Lys Ala Gly Lys Asp
610 615 620

Glu Gln Lys Glu Glu Glu Lys Val Glu Glu Lys Lys Glu Val Ala Lys
625 630 635 640

Glu Ser Pro Lys Glu Glu Lys Val Glu Lys Lys Glu Glu Lys Pro Lys
645 650 655

Asp Val Pro Asp Lys Lys Lys Ala Glu Ser Pro Val Lys Glu Lys Ala
660 665 670

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Val Glu Glu Met Ile Thr Ile Thr Lys Ser Val Lys Val Ser Leu Glu
        675                 680                 685

Lys Asp Thr Lys Glu Glu Lys Pro Gln Gln Gln Glu Lys Val Lys Glu
    690                 695                 700

Lys Ala Glu Glu Glu Gly Gly Ser Glu Glu Glu Val Gly Asp Lys Ser
705                 710                 715                 720

Pro Gln Glu Ser Lys Lys Glu Asp Ile Ala Ile Asn Gly Glu Val Glu
                725                 730                 735

Gly Lys Glu Glu Glu Glu Gln Glu Thr Gln Glu Lys Gly Ser Gly Gln
            740                 745                 750

Glu Glu Glu Lys Gly Val Val Thr Asn Gly Leu Asp Val Ser Pro Ala
        755                 760                 765

Glu Glu Lys Lys Gly Glu Asp Arg Ser Asp Asp Lys Val Val Val Thr
    770                 775                 780

Lys Lys Val Glu Lys Ile Thr Ser Glu Gly Gly Asp Gly Ala Thr Lys
785                 790                 795                 800

Tyr Ile Thr Lys Ser Val Thr Val Thr Gln Lys Val Glu Glu His Glu
                805                 810                 815

Glu Thr Phe Glu Glu Lys Leu Val Ser Thr Lys Lys Val Glu Lys Val
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Thr Ser His Ala Ile Val Lys Glu Val Thr Gln Gly Asp
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<213> Rattus norvegicus

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<400> 62

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<213> Rattus norvegicus

<220>
<223> Neurodegeneration associated protein 1

<400> 63

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Gly Arg Arg Tyr Gly Arg Arg His Ala Tyr Val Ser Phe Lys Pro Cys
        35                  40                  45

Met Thr Arg His Glu Arg Ser Leu Gly Arg Ala Gly Asp Asp Tyr Glu
    50                  55                  60

Val Leu Glu Leu Asp Asp Val Ala Lys Glu Asn Thr Ala Gly Ser Ser
65                  70                  75                  80

Ser Leu Asp Gln Val His Pro Ser Leu Pro Ser Glu Thr Thr Val Glu
                85                  90                  95

Lys Ser Glu Thr Glu Ile Pro Thr Cys Gly Pro Ala Leu Asn Gln Ser
            100                 105                 110

Thr Glu Ser Asn Pro Ser Val Ala Thr Val Cys His Ser Glu Glu Val
        115                 120                 125
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Arg Glu Thr Leu Asp Ser Ser Thr Asn Leu Gln Asn His Ala Glu Arg
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Glu Cys Thr Pro Ala Val Cys Asn Ala Ser Ser Val Gln Asn Gly Ile
145                 150                 155                 160

Val Leu Val His Thr Asp Ser Tyr Asp Pro Asp Ser Lys His Asp Glu
                165                 170                 175

Asn Asp Ser Leu Gln Leu Cys Ala Gln Ala Val Glu Gly Gly Arg Arg
            180                 185                 190

Gln Lys Val Leu Gly Asn Ala Val Phe Glu Leu Glu Asn Gly Glu Val
        195                 200                 205

Glu Arg Tyr Ala Asp Leu Cys Pro Ser Val Pro Ser Leu Ser Gly Glu
    210                 215                 220

Ile Arg Glu Glu Ser Glu Glu Leu Gly Ser Ala Leu Leu Glu Lys Asn
225                 230                 235                 240

Ser Ala Gly Asp Ala Glu Ala Val His Gln Asp Gly Gln Glu Phe Gln
                245                 250                 255

Arg Ser Ser Glu Asp Gly Ile Val Arg Lys Arg Arg Gln Asp Asp Thr
            260                 265                 270

Asp Gln Gly Arg Gln Thr Glu Asn Ser Thr Glu Asp Ala Asp Cys Val
        275                 280                 285

Pro Gly His Val Glu Gln Asn Thr Ser Glu Arg Ala Asn His His Gly
    290                 295                 300

Ser Ser Pro Glu Gln Val Val Arg Pro Lys Val Arg Lys Val Ile Ser
305                 310                 315                 320

Ser Ser Gln Val Asp Gln Glu Ser Gly Phe Asn Arg His Glu Ala Lys
                325                 330                 335

Gln Arg Ser Val Gln Arg Trp Arg Glu Ala Leu Glu Val Glu Glu Cys
            340                 345                 350

Ser Ser Asp Asp Pro Ile Ile Lys Cys Asp Asp Tyr Asp Gly Asp His
        355                 360                 365

Asp Cys Met Phe Leu Thr Pro Ser Tyr Ser Arg Val Thr Pro Arg Glu
    370                 375                 380

Ala Glu Arg His Arg Ala Thr Ala Glu Asn Gly Ala Thr Ala Ser Gly
385                 390                 395                 400

Arg Gln Glu Ala Arg Glu Asn Ala Phe Trp Asn Ala Cys Gly Glu Tyr
                405                 410                 415

Tyr Gln Leu Phe Asp Lys Asp Glu Asp Ser Ser Glu Cys Ser Asp Gly
            420                 425                 430

Glu Trp Ser Ala Ser Leu Pro His Arg Phe Ser Gly Thr Glu Lys Asp
        435                 440                 445

Gln Ser Ser Ser Asp Glu Ser Trp Glu Thr Leu Pro Gly Lys Asp Glu
    450                 455                 460
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Asn Glu Pro Glu Leu Gln Ser Asp Ser Ser Gly Pro Glu Glu Glu Asn
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Gln Glu Leu Ser Leu Gln Glu Gly Glu Gln Thr Ser Leu Glu Glu Gly
485 490 495

Glu Ile Pro Trp Leu Gln Tyr Asn Glu Val Asn Glu Ser Ser Ser Asp
500 505 510

Glu Gly Asn Glu Pro Ala Asn Glu Phe Ala Gln Pro Glu Ala Phe Met
515 520 525

Leu Asp Gly Asn Asn Asn Leu Glu Asp Asp Ser Ser Val Ser Glu Asp
530 535 540

Leu Asp Val Asp Trp Ser Leu Phe Asp Gly Phe Ala Asp Gly Leu Gly
545 550 555 560

Val Ala Glu Ala Ile Ser Tyr Val Asp Pro Gln Phe Leu Thr Tyr Met
565 570 575

Ala Leu Glu Glu Arg Leu Ala Gln Ala Met Glu Thr Ala Leu Ala His
580 585 590

Leu Glu Ser Leu Ala Val Asp Val Glu Val Ala Asn Pro Pro Ala Ser
595 600 605

Lys Glu Ser Ile Asp Gly Leu Pro Glu Thr Leu Val Leu Glu Asp His
610 615 620

Thr Ala Ile Gly Gln Glu Gln Cys Cys Pro Ile Cys Cys Ser Glu Tyr
625 630 635 640

Ile Lys Asp Asp Ile Ala Thr Glu Leu Pro Cys His His Phe Phe His
645 650 655

Lys Pro Cys Val Ser Ile Trp Leu Gln Lys Ser Gly Thr Cys Pro Val
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Cys Arg Arg His Phe Pro Pro Ala Val Ile Asp Ala Ser Ala Ala Ala
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Glu Ala Pro
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Ile Thr Asp Ala Ala Arg His Lys Leu Leu Val Leu Thr Gly Gln Cys
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Phe Glu Asn Thr Gly Glu Leu Ile Leu Gln Ser Gly Ser Phe Ser Phe
    50                  55                  60

Gln Asn Phe Ile Glu Ile Phe Thr Asp Gln Glu Ile Gly Glu Leu Leu
65                  70                  75                  80

Ser Thr Thr His Pro Ala Asn Lys Ala Ser Leu Thr Leu Phe Cys Pro
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Glu Glu Gly Asp Trp Lys Asn Ser Asn Leu Asp Arg His Asn Leu Gln
            100                 105                 110

Asp Phe Ile Asn Ile Lys Leu Asn Ser Ala Ser Ile Leu Pro Glu Met
        115                 120                 125

Glu Gly Leu Ser Glu Phe Thr Glu Tyr Leu Ser Glu Ser Val Glu Val
    130                 135                 140

Pro Ser Pro Phe Asp Ile Leu Glu Pro Pro Thr Ser Gly Gly Phe Leu
145                 150                 155                 160

Lys Leu Ser Lys Pro Cys Cys Tyr Ile Phe Pro Gly Gly Arg Gly Asp
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Ser Ala Leu Phe Ala Val Asn Gly Phe Asn Met Leu Ile Asn Gly Gly
            180                 185                 190

Ser Glu Arg Lys Ser Cys Phe Trp Lys Leu Ile Arg His Leu Asp Arg
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Val Asp Ser Ile Leu Leu Thr His Ile Gly Asp Asp Asn Leu Pro Gly
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Ile Asn Ser Met Leu Gln Arg Lys Ile Ala Glu Leu Glu Glu Glu Ser
225                 230                 235                 240

Gln Gly Ser Thr Ser Asn Ser Asp Trp Met Lys Asn Leu Ile Ser Pro
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Asp Leu Gly Val Val Phe Leu Asn Val Pro Glu Asn Leu Lys Asn Pro
            260                 265                 270

Glu Pro Asn Ile Lys Met Lys Arg Ser Thr Glu Glu Ala Cys Phe Thr
        275                 280                 285

Leu Gln Tyr Leu Asn Lys Leu Ser Met Lys Pro Glu Pro Leu Phe Arg
    290                 295                 300

Ser Val Gly Asn Ala Ile Glu Pro Val Ile Leu Phe Gln Lys Met Gly
305                 310                 315                 320

Val Gly Lys Leu Lys Met Tyr Val Leu Asn Pro Val Lys Ser Ser Lys
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Ala Glu Leu Ile Leu Pro Asn Gly Gln Glu Val Asp Ile Pro Ile Ser
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Tyr Leu Ala Ser Val Ser Ser Leu Ile Val Trp His Pro Ala Asn Pro
    370                 375                 380

Ala Glu Lys Ile Ile Arg Val Leu Phe Pro Gly Asn Ser Thr Gln Tyr
385                 390                 395                 400

Asn Ile Leu Glu Gly Leu Glu Lys Leu Lys His Leu Asp Phe Leu Lys
                405                 410                 415

Gln Pro Leu Ala Thr Gln Lys Asp Leu Thr Gly Gln Val Ser Thr Pro
            420                 425                 430

Pro Val Lys Gln Val Lys Leu Lys Gln Arg Ala Asp Ser Arg Glu Ser
        435                 440                 445

Leu Lys Pro Ala Thr Lys Pro Leu Ser Ser Lys Ser Val Arg Lys Glu
    450                 455                 460

Ser Lys Glu Glu Ala Pro Glu Ala Thr Lys Ala Ser Gln Val Glu Lys
465                 470                 475                 480

Thr Pro Lys Val Glu Ser Lys Glu Lys Val Ile Val Lys Lys Asp Lys
                485                 490                 495

Pro Gly Lys Val Glu Ser Lys Pro Ser Val Thr Glu Lys Glu Val Pro
            500                 505                 510

Ser Lys Glu Glu Gln Ser Pro Val Lys Ala Glu Val Ala Glu Lys Ala
        515                 520                 525

Ala Thr Glu Ser Lys Pro Lys Val Thr Lys Asp Lys Val Val Lys Lys
    530                 535                 540

Glu Ile Lys Thr Lys Pro Glu Glu Lys Lys Glu Glu Lys Pro Lys Lys
545                 550                 555                 560

Glu Val Ala Lys Lys Glu Asp Lys Thr Pro Leu Lys Lys Asp Glu Lys
                565                 570                 575

Pro Lys Lys Glu Glu Ala Lys Lys Glu Ile Lys Lys Glu Ile Lys Lys
            580                 585                 590

Glu Glu Lys Lys Glu Leu Lys Lys Glu Val Lys Lys Glu Thr Pro Leu
        595                 600                 605

Lys Asp Ala Lys Lys Glu Val Lys Lys Asp Glu Lys Lys Glu Val Lys
    610                 615                 620

Lys Glu Glu Lys Glu Pro Lys Lys Glu Ile Lys Lys Ile Ser Lys Asp
625                 630                 635                 640

Ile Lys Lys Ser Thr Pro Leu Ser Asp Thr Lys Lys Pro Ala Ala Leu
                645                 650                 655

Lys Pro Lys Val Ala Lys Lys Glu Glu Pro Thr Lys Lys Glu Pro Ile
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Ala Ala Gly Lys Leu Lys Asp Lys Gly Lys Val Lys Val Ile Lys Lys
675 680 685

Glu Gly Lys Thr Thr Glu Ala Ala Ala Thr Ala Val Gly Thr Ala Ala
690 695 700

Val Ala Ala Ala Ala Gly Val Ala Ala Ser Gly Pro Ala Lys Glu Leu
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Glu Ala Glu Arg Ser Leu Met Ser Ser Pro Glu Asp Leu Thr Lys Asp
725 730 735

Phe Glu Glu Leu Lys Ala Glu Glu Ile Asp Val Ala Lys Asp Ile Lys
740 745 750

Pro Gln Leu Glu Leu Ile Glu Asp Glu Glu Lys Leu Lys Glu Thr Glu
755 760 765

Pro Gly Glu Ala Tyr Val Ile Gln Lys Glu Thr Glu Val Ser Lys Gly
770 775 780

Ser Ala Glu Ser Pro Asp Glu Gly Ile Thr Thr Thr Glu Gly Glu Gly
785 790 795 800

Glu Cys Glu Gln Thr Pro Glu Glu Leu Glu Pro Val Glu Lys Gln Gly
805 810 815

Val Asp Asp Ile Glu Lys Phe Glu Asp Glu Gly Ala Gly Phe Glu Glu
820 825 830

Ser Ser Glu Ala Gly Asp Tyr Glu Glu Lys Ala Glu Thr Glu Glu Ala
835 840 845

Glu Glu Pro Glu Glu Asp Gly Glu Asp Asn Val Ser Gly Ser Ala Ser
850 855 860

Lys His Ser Pro Thr Glu Asp Glu Glu Ile Ala Lys Ala Glu Ala Asp
865 870 875 880

Val His Ile Lys Glu Lys Arg Glu Ser Val Ala Ser Gly Asp Asp Arg
885 890 895

Ala Glu Glu Asp Met Asp Glu Ala Leu Glu Lys Gly Glu Ala Glu Gln
900 905 910

Ser Glu Glu Glu Gly Glu Glu Glu Glu Asp Lys Ala Glu Asp Ala Arg
915 920 925

Glu Glu Asp His Glu Pro Asp Lys Thr Glu Ala Glu Asp Tyr Val Met
930 935 940

Ala Val Val Asp Lys Ala Ala Glu Ala Gly Val Thr Glu Asp Gln Tyr
945 950 955 960

Asp Phe Leu Gly Thr Pro Ala Lys Gln Pro Gly Val Gln Ser Pro Ser
965 970 975

Arg Glu Pro Ala Ser Ser Ile His Asp Glu Thr Leu Pro Gly Gly Ser
980 985 990

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Glu Glu Phe Thr Ala Thr Ser Gly Tyr Thr Gln Ser Thr Ile Glu Ile
   1010                1015                1020

Ser Ser Glu Pro Thr Pro Met Asp Glu Met Ser Thr Pro Arg Asp Val
1025                1030                1035                1040

Met Thr Asp Glu Thr Asn Asn Glu Glu Thr Glu Ser Pro Ser Gln Glu
                1045                1050                1055

Phe Val Asn Ile Thr Lys Tyr Glu Ser Ser Leu Tyr Ser Gln Glu Tyr
            1060                1065                1070

Ser Lys Pro Val Val Ala Ser Phe Asn Gly Leu Ser Asp Gly Ser Lys
        1075                1080                1085

Thr Asp Ala Thr Asp Gly Arg Asp Tyr Asn Ala Ser Ala Ser Thr Ile
   1090                1095                1100

Ser Pro Pro Ser Ser Met Glu Glu Asp Lys Phe Ser Lys Ser Ala Leu
1105                1110                1115                1120

Arg Asp Ala Tyr Arg Pro Glu Glu Thr Asp Val Lys Thr Gly Ala Glu
                1125                1130                1135

Leu Asp Ile Lys Asp Val Ser Asp Glu Arg Leu Ser Pro Ala Lys Ser
            1140                1145                1150

Pro Ser Leu Ser Pro Ser Pro Pro Ser Pro Ile Glu Lys Thr Pro Leu
        1155                1160                1165

Gly Glu Arg Ser Val Asn Phe Ser Leu Thr Pro Asn Glu Ile Lys Ala
   1170                1175                1180

Ser Ala Glu Gly Glu Ala Thr Ala Val Val Ser Pro Gly Val Thr Gln
1185                1190                1195                1200

Ala Val Val Glu Glu His Cys Ala Ser Pro Glu Glu Lys Thr Leu Glu
                1205                1210                1215

Val Val Ser Pro Ser Gln Ser Val Thr Gly Ser Ala Gly His Thr Pro
            1220                1225                1230

Tyr Tyr Gln Ser Pro Thr Asp Glu Lys Ser Ser His Leu Pro Thr Glu
        1235                1240                1245

Val Thr Glu Asn Ala Gln Ala Val Pro Val Ser Phe Glu Phe Thr Glu
   1250                1255                1260

Ala Lys Asp Glu Asn Glu Arg Ser Ser Ile Ser Pro Met Asp Glu Pro
1265                1270                1275                1280

Val Pro Asp Ser Glu Ser Pro Ile Glu Lys Val Leu Ser Pro Leu Arg
                1285                1290                1295

Ser Pro Pro Leu Ile Gly Ser Glu Ser Ala Tyr Glu Asp Phe Leu Ser
            1300                1305                1310

Ala Asp Asp Lys Ala Leu Gly Arg Arg Ser Glu Ser Pro Phe Glu Gly
        1315                1320                1325
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Lys Asn Gly Lys Gln Gly Phe Ser Asp Lys Glu Ser Pro Val Ser Asp
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Leu Thr Ser Asp Leu Tyr Gln Asp Lys Gln Glu Glu Lys Arg Ala Gly
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Phe Ile Pro Ile Lys Glu Asp Phe Ser Pro Glu Lys Lys Ala Ser Asp
                1365                1370                1375

Ala Glu Ile Met Ser Ser Gln Ser Ala Leu Ala Leu Asp Glu Arg Lys
           1380                1385                1390

Leu Gly Gly Asp Gly Ser Pro Thr Gln Val Asp Val Ser Gln Phe Gly
       1395                1400                1405

Ser Phe Lys Glu Asp Thr Lys Met Ser Ile Ser Glu Gly Thr Val Ser
   1410                1415                1420

Asp Lys Ser Ala Thr Pro Val Asp Glu Gly Ala Glu Asp Thr Tyr Ser
1425                1430                1435                1440

His Met Glu Gly Val Ala Ser Val Ser Thr Ala Ser Val Ala Thr Ser
                1445                1450                1455

Ser Phe Pro Glu Pro Thr Thr Asp Asp Val Ser Pro Ser Leu His Ala
           1460                1465                1470

Glu Val Gly Ser Pro His Ser Thr Glu Val Asp Asp Ser Leu Ser Val
       1475                1480                1485

Ser Val Val Gln Thr Pro Thr Thr Phe Gln Glu Thr Glu Met Ser Pro
   1490                1495                1500

Ser Lys Glu Glu Cys Pro Arg Pro Met Ser Ile Ser Pro Pro Asp Phe
1505                1510                1515                1520

Ser Pro Lys Thr Ala Lys Ser Arg Thr Pro Val Gln Asp His Arg Ser
                1525                1530                1535

Glu Gln Ser Ser Met Ser Ile Glu Phe Gly Gln Glu Ser Pro Glu His
           1540                1545                1550

Ser Leu Ala Met Asp Phe Ser Arg Gln Ser Pro Asp His Pro Thr Val
       1555                1560                1565

Gly Ala Gly Met Leu His Ile Thr Glu Asn Gly Pro Thr Glu Val Asp
   1570                1575                1580

Tyr Ser Pro Ser Asp Ile Gln Asp Ser Ser Leu Ser His Lys Ile Pro
1585                1590                1595                1600

Pro Thr Glu Glu Pro Ser Tyr Thr Gln Asp Asn Asp Leu Ser Glu Leu
                1605                1610                1615

Ile Ser Val Ser Gln Val Glu Ala Ser Pro Ser Thr Ser Ser Ala His
           1620                1625                1630

Thr Pro Ser Gln Ile Ala Ser Pro Leu Gln Glu Asp Thr Leu Ser Asp
       1635                1640                1645

Val Val Pro Pro Arg Asp Met Ser Leu Tyr Ala Ser Leu Ala Ser Glu
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Lys Val Gln Ser Leu Glu Gly Glu Lys Leu Ser Pro Lys Ser Asp Ile
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Ser Pro Leu Thr Pro Arg Glu Ser Ser Pro Thr Tyr Ser Pro Gly Phe
                1685                1690                1695

Ser Asp Ser Thr Ser Gly Ala Lys Glu Ser Thr Ala Ala Tyr Gln Thr
            1700                1705                1710

Ser Ser Ser Pro Pro Ile Asp Ala Ala Ala Ala Glu Pro Tyr Gly Phe
        1715                1720                1725

Arg Ser Ser Met Leu Phe Asp Thr Met Gln His His Leu Ala Leu Ser
    1730                1735                1740

Arg Asp Leu Thr Thr Ser Ser Val Glu Lys Asp Asn Gly Gly Lys Thr
1745                1750                1755                1760

Pro Gly Asp Phe Asn Tyr Ala Tyr Gln Lys Pro Glu Ser Thr Thr Glu
                1765                1770                1775

Ser Pro Asp Glu Glu Asp Tyr Asp Tyr Glu Ser His Glu Lys Thr Ile
            1780                1785                1790

Gln Ala His Asp Val Gly Gly Tyr Tyr Tyr Glu Lys Thr Glu Arg Thr
        1795                1800                1805

Ile Lys Ser Pro Cys Asp Ser Gly Tyr Ser Tyr Glu Thr Ile Glu Lys
    1810                1815                1820

Thr Thr Lys Thr Pro Glu Asp Gly Gly Tyr Ser Cys Glu Ile Thr Glu
1825                1830                1835                1840

Lys Thr Thr Arg Thr Pro Glu Glu Gly Gly Tyr Ser Tyr Glu Ile Ser
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Glu Lys Thr Thr Arg Thr Pro Glu Val Ser Gly Tyr Thr Tyr Glu Lys
            1860                1865                1870

Thr Glu Arg Ser Arg Arg Leu Leu Asp Asp Ile Ser Asn Gly Tyr Asp
        1875                1880                1885

Asp Thr Glu Asp Gly Gly His Thr Leu Gly Asp Cys Ser Tyr Ser Tyr
    1890                1895                1900

Glu Thr Thr Glu Lys Ile Thr Ser Phe Pro Glu Ser Glu Ser Tyr Ser
1905                1910                1915                1920

Tyr Glu Thr Thr Thr Lys Thr Thr Arg Ser Pro Asp Thr Ser Ala Tyr
                1925                1930                1935

Cys Tyr Glu Thr Met Glu Lys Ile Thr Lys Thr Pro Gln Ala Ser Thr
            1940                1945                1950

Tyr Ser Tyr Glu Thr Ser Asp Arg Cys Tyr Thr Pro Glu Arg Lys Ser
        1955                1960                1965

Pro Ser Glu Ala Arg Gln Asp Val Asp Leu Cys Leu Val Ser Ser Cys
    1970                1975                1980
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Glu Phe Lys His Pro Lys Thr Glu Leu Ser Pro Ser Phe Ile Asn Pro
1985 1990 1995 2000

Asn Pro Leu Glu Trp Phe Ala Gly Glu Glu Pro Thr Glu Glu Ser Glu
2005 2010 2015

Arg Pro Leu Thr Gln Ser Gly Gly Ala Pro Pro Pro Ser Gly Gly Lys
2020 2025 2030

Gln Gln Gly Arg Gln Cys Asp Glu Thr Pro Pro Thr Ser Val Ser Glu
2035 2040 2045

Ser Ala Pro Ser Gln Thr Asp Ser Asp Val Pro Pro Glu Thr Glu Glu
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Cys Pro Ser Ile Thr Ala Asp Ala Asn Leu Asp Ser Glu Asp Glu Ser
2065 2070 2075 2080

Glu Thr Ile Pro Thr Asp Lys Thr Val Thr Tyr Lys His Met Asp Pro
2085 2090 2095

Pro Pro Ala Pro Met Gln Asp Arg Ser Pro Ser Pro Arg His Pro Asp
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Val Ser Met Val Asp Pro Glu Ala Leu Ala Ile Glu Gln Asn Leu Gly
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Lys Ala Leu Lys Lys Asp Leu Lys Glu Lys Ala Lys Thr Lys Lys Pro
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Gly Thr Lys Thr Lys Ser Ser Ser Pro Val Lys Lys Gly Asp Gly Lys
2145 2150 2155 2160

Ser Lys Pro Ser Ala Ala Ser Pro Lys Pro Gly Ala Leu Lys Glu Ser
2165 2170 2175

Ser Asp Lys Val Ser Arg Val Ala Ser Pro Lys Lys Lys Glu Ser Val
2180 2185 2190

Glu Lys Ala Met Lys Thr Thr Thr Thr Pro Glu Val Lys Ala Thr Arg
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Cys Tyr Ile Pro Asn His Ser Asn Ser Lys Asn Val Asp Val Glu Phe
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Phe Lys Arg Val Arg Ser Ser Tyr Tyr Val Val Ser Gly Asn Asp Pro
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Ala Ala Glu Glu Pro Ser Arg Ala Val Leu Asp Ala Leu Leu Glu Gly
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Lys Ala Gln Trp Gly Ser Asn Met Gln Val Thr Leu Ile Pro Thr His
2305 2310 2315 2320

Asp Ser Glu Val Met Arg Glu Trp Tyr Gln Glu Thr His Glu Lys Gln
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<213> Rattus norvegicus

<220>
<223> Microtubule associated protein IB

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<213> Rattus norvegicus

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<223> cdc 37 homolog

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Met Pro Trp Asn Val Asp Thr Leu Ser Lys Asp Gly Phe Ser Lys Ser
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Met Val Asn Thr Lys Pro Glu Lys Ala Glu Glu Asp Ser Glu Glu Ala
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Ser Asp Asn Val His Leu Val Cys Glu Glu Thr Ala Asn Tyr Leu Val
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Ala Ile Ser Lys Met Asp Pro Thr Asp Ala Lys Tyr His Met Gln Arg
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Cys Ile Asp Ser Gly Leu Trp Val Pro Asn Ser Lys Ser Gly Glu Ala
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Asn Leu Tyr Gly Asp Phe Phe Thr Gly Asp Ala Tyr Val Ile Leu Lys
35 40 45

Thr Val Gln Leu Arg Asn Gly Asn Leu Gln Tyr Asp Leu His Tyr Trp
50 55 60

Leu Gly Asn Glu Cys Ser Gln Asp Glu Ser Gly Ala Ala Ala Ile Phe

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65                  70                  75                  80

Thr Val Gln Leu Asp Asp Tyr Leu Asn Gly Arg Ala Val Gln His Arg
                85                  90                  95

Glu Val Gln Gly Phe Glu Ser Ser Thr Phe Ser Gly Tyr Phe Lys Ser
            100                 105                 110

Gly Leu Lys Tyr Lys Lys Gly Gly Val Ala Ser Gly Phe Lys His Val
        115                 120                 125

Val Pro Asn Glu Val Val Val Gln Arg Leu Phe Gln Val Lys Gly Arg
    130                 135                 140

Arg Val Val Arg Ala Thr Glu Val Pro Val Ser Trp Asp Ser Phe Asn
145                 150                 155                 160

Asn Gly Asp Cys Phe Ile Leu Asp Leu Gly Asn Asn Ile Tyr Gln Trp
                165                 170                 175

Cys Gly Ser Gly Ser Asn Lys Phe Glu Arg Leu Lys Ala Thr Gln Val
            180                 185                 190

Ser Lys Gly Ile Arg Asp Asn Glu Arg Ser Gly Arg Ala Gln Val His
        195                 200                 205

Val Ser Glu Glu Glu Thr Glu Pro Glu Ala Met Leu Gln Val Leu Gly
    210                 215                 220

Pro Lys Pro Ala Leu Pro Glu Gly Thr Glu Asp Thr Ala Lys Glu Asp
225                 230                 235                 240

Ala Ala Asn Arg Lys Leu Ala Lys Leu Tyr Lys Val Ser Asn Gly Ala
                245                 250                 255

Gly Ser Met Ser Val Ser Leu Val Ala Asp Glu Asn Pro Phe Ala Gln
            260                 265                 270

Gly Pro Leu Arg Ser Glu Asp Cys Phe Ile Leu Asp His Gly Arg Asp
        275                 280                 285

Gly Lys Ile Phe Val Trp Lys Gly Lys Gln Ala Asn Met Glu Glu Arg
    290                 295                 300

Lys Ala Ala Leu Lys Thr Ala Ser Asp Phe Ile Ser Lys Met Gln Tyr
305                 310                 315                 320

Pro Arg Gln Thr Gln Val Ser Val Leu Pro Glu Gly Gly Glu Thr Pro
                325                 330                 335

Leu Phe Lys Gln Phe Phe Lys Asn Trp Arg Asp Pro Asp Gln Thr Asp
            340                 345                 350

Gly Pro Gly Leu Gly Tyr Leu Ser Ser His Ile Ala Asn Val Glu Arg
        355                 360                 365

Val Pro Phe Asp Ala Gly Thr Leu His Thr Ser Thr Ala Met Ala Ala
    370                 375                 380

Gln His Gly Met Asp Asp Asp Gly Thr Gly Gln Lys Gln Ile Trp Arg
385                 390                 395                 400
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Ile Glu Gly Ser Asn Lys Val Pro Val Asp Pro Ala Thr Tyr Gly Gln
                405                 410                 415

Phe Tyr Gly Gly Asp Ser Tyr Ile Ile Leu Tyr Asn Tyr Arg His Gly
            420                 425                 430

Gly Arg Gln Gly Gln Ile Ile Tyr Asn Trp Gln Gly Ala Gln Ser Thr
        435                 440                 445

Gln Asp Glu Val Ala Ala Ser Ala Ile Leu Thr Ala Gln Leu Asp Glu
    450                 455                 460

Glu Leu Gly Gly Thr Pro Val Gln Ser Arg Val Val Gln Gly Lys Glu
465                 470                 475                 480

Pro Ala His Leu Met Ser Leu Phe Gly Gly Lys Pro Met Ile Ile Tyr
                485                 490                 495

Lys Gly Gly Thr Ser Arg Asp Gly Gly Gln Thr Ala Pro Ala Ser Ile
            500                 505                 510

Arg Leu Phe Gln Val Arg Ala Ser Ser Ser Gly Ala Thr Arg Ala Val
        515                 520                 525

Glu Val Met Pro Lys Ser Gly Ala Leu Asn Ser Asn Asp Ala Phe Val
    530                 535                 540

Leu Lys Thr Pro Ser Ala Ala Tyr Leu Trp Val Gly Ala Gly Ala Ser
545                 550                 555                 560

Glu Ala Glu Lys Thr Ala Ala Gln Glu Leu Leu Lys Val Leu Arg Ser
                565                 570                 575

Gln His Val Gln Val Glu Clu Gly Ser Glu Pro Asp Gly Phe Trp Glu
            580                 585                 590

Ala Leu Gly Gly Lys Thr Ser Tyr Arg Thr Ser Pro Arg Leu Lys Asp
        595                 600                 605

Lys Lys Met Asp Ala His Pro Pro Arg Leu Phe Ala Cys Ser Asn Arg
    610                 615                 620

Ile Gly Arg Phe Val Ile Glu Glu Val Pro Gly Glu Leu Met Gln Glu
625                 630                 635                 640

Asp Leu Ala Thr Asp Asp Val Met Leu Leu Asp Thr Trp Asp Gln Val
                645                 650                 655

Phe Val Trp Val Gly Lys Asp Ser Gln Glu Glu Glu Lys Thr Glu Ala
            660                 665                 670

Leu Thr Ser Ala Lys Arg Tyr Ile Glu Thr Asp Pro Ala Asn Arg Asp
        675                 680                 685

Arg Arg Thr Pro Ile Thr Val Val Arg Gln Gly Phe Glu Pro Pro Ser
    690                 695                 700

Phe Val Gly Trp Phe Leu Gly Trp Asp Asn Asn Tyr Trp Ser Val Asp
705                 710                 715                 720

Pro Leu Asp Arg Ala Leu Ala Glu Leu Ala Ala
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<210> 73
<211> 2447
<212> DNA
<213> Mus musculus

<220>
<223> Gelsolin

<400> 73
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tatggagact tcttcacggg tgatgcctat gtcatcctga agactgtgca gctgaggaat 180
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caccgtgagg ttcagggctt tgagtcgtcc accttctccg gctacttcaa gtctggactt 360
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<210> 74
<211> 236
<212> PRT
<213> Rattus norvegicus

<220>
<223> Cd81 antigen

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Phe Asn Phe Val Phe Trp Leu Ala Gly Gly Val Ile Leu Gly Val Ala
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Leu Trp Leu Arg His Asp Pro Gln Thr Thr Thr Leu Leu Tyr Leu Glu
35 40 45

Leu Gly Asp Lys Pro Ala Pro Ser Thr Phe Tyr Val Gly Ile Tyr Ile
50 55 60

Leu Ile Ala Val Gly Ala Val Met Met Phe Val Gly Phe Leu Gly Cys
65 70 75 80

Tyr Gly Ala Ile Gln Glu Ser Gln Cys Leu Leu Gly Thr Phe Phe Thr
85 90 95

Cys Leu Val Ile Leu Phe Ala Cys Glu Val Ala Ala Gly Ile Trp Gly
100 105 110

Phe Val Asn Lys Asp Gln Ile Ala Lys Asp Val Lys Gln Phe Tyr Asp
115 120 125

Gln Ala Leu Gln Gln Ala Val Met Asp Asp Asp Ala Asn Asn Ala Lys
130 135 140

Ala Val Val Lys Thr Phe His Glu Thr Leu Asn Cys Cys Gly Ser Asn
145 150 155 160

Thr Leu Thr Thr Leu Thr Thr Ala Val Leu Arg Asn Ser Leu Cys Pro
165 170 175

Ser Ser Ser Asn Ser Phe Thr Gln Leu Leu Lys Glu Asp Cys His Gln
180 185 190

Lys Ile Asp Glu Leu Phe Ser Gly Lys Leu Tyr Leu Ile Gly Ile Ala
195 200 205

Ala Ile Val Val Ala Val Ile Met Ile Phe Glu Met Ile Leu Ser Met
210 215 220

Val Leu Cys Cys Gly Ile Arg Asn Ser Ser Val Tyr
225 230 235

<210> 75
<211> 1303
<212> DNA
<213> Rattus norvegicus

<220>
<223> Cd81 antigen

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<212> PRT
<213> Rattus norvegicus

<220>
<223> MOBP-81 protein

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Lys Phe Ser Glu His Phe Ser Ile His Cys Cys Pro Pro Phe Thr Phe
20 25 30

Leu Asn Ser Lys Arg Glu Ile Val Asp Arg Lys Tyr Ser Ile Cys Lys
35 40 45

Ser Gly Cys Phe Tyr Gln Lys Lys Glu Glu Asp Trp Ile Cys Cys Ala
50 55 60

Cys Gln Lys Thr Arg Leu Arg Arg Arg Ser Arg Ser Thr Pro Arg Lys
65 70 75 80

Lys

<210> 77
<211> 2405
<212> DNA
<213> Rattus norvegicus

<220>
<223> MOBP-81 protein

<400> 77
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ggccaaggag ggccccaggc tctccaagaa ccagaagttc tcagagcact tcagcatcca 180
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catctgcaag agcggttgct tttaccagaa gaaggaggag gactggatct gctgtgcctg 300
ccagaagacc agattgagaa ggaggagcag gtcaacccca agaaaaaagt gaccgagaag 360
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<210> 78
<211> 590
<212> PRT
<213> Homo sapiens

<220>
<223> Syntaxin binding protein 2

<400> 78

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Gly Val Ile Arg Ser Val Lys Lys Asp Gly Glu Trp Lys Val Leu Ile
            20                  25                  30

Met Asp His Pro Ser Met Arg Ile Leu Ser Ser Cys Cys Lys Met Ser
        35                  40                  45

Asp Ile Leu Ala Glu Gly Ile Thr Ile Val Glu Asp Ile Asn Lys Arg
    50                  55                  60

Arg Glu Pro Ile Pro Ser Leu Glu Ala Ile Tyr Leu Leu Ser Pro Thr
65                  70                  75                  80

Glu Lys Ala Leu Ile Lys Asp Phe Gln Gly Thr Pro Thr Phe Thr Tyr
                85                  90                  95
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Lys Ala Ala His Ile Phe Phe Thr Asp Thr Cys Pro Glu Pro Leu Phe
            100                 105                 110

Ser Glu Leu Gly Arg Ser Arg Leu Ala Lys Val Val Lys Thr Leu Lys
        115                 120                 125

Glu Ile His Leu Ala Phe Leu Pro Tyr Glu Ala Gln Val Phe Ser Leu
    130                 135                 140

Asp Ala Pro His Ser Thr Tyr Asn Leu Tyr Cys Pro Phe Arg Ala Glu
145                 150                 155                 160

Glu Arg Thr Arg Gln Leu Glu Val Leu Ala Gln Gln Ile Ala Thr Leu
                165                 170                 175

Cys Ala Thr Leu Gln Glu Tyr Pro Ala Ile Arg Tyr Arg Lys Gly Pro
            180                 185                 190

Glu Asp Thr Ala Gln Leu Ala His Ala Val Leu Ala Lys Leu Asn Ala
        195                 200                 205

Phe Lys Ala Asp Thr Pro Ser Leu Gly Glu Gly Pro Glu Lys Thr Arg
    210                 215                 220

Ser Gln Leu Leu Ile Met Asp Arg Ala Ala Asp Pro Val Ser Pro Leu
225                 230                 235                 240

Leu His Glu Leu Thr Phe Gln Ala Met Ala Tyr Asp Leu Leu Asp Ile
                245                 250                 255

Glu Gln Asp Thr Tyr Arg Tyr Glu Thr Thr Gly Leu Ser Glu Ala Arg
            260                 265                 270

Glu Lys Ala Val Leu Leu Asp Glu Asp Asp Asp Leu Trp Val Glu Leu
        275                 280                 285

Arg His Met His Ile Ala Asp Val Ser Lys Lys Val Thr Glu Leu Leu
    290                 295                 300

Arg Thr Phe Cys Glu Ser Lys Arg Leu Thr Thr Asp Lys Ala Asn Ile
305                 310                 315                 320

Lys Asp Leu Ser Gln Ile Leu Lys Lys Met Pro Gln Tyr Gln Lys Glu
                325                 330                 335

Leu Asn Lys Tyr Ser Thr His Leu His Leu Ala Asp Asp Cys Met Lys
            340                 345                 350

His Phe Lys Gly Ser Val Glu Lys Leu Cys Ser Val Glu Gln Asp Leu
        355                 360                 365

Ala Met Gly Ser Asp Ala Glu Gly Glu Lys Ile Lys Asp Ser Met Lys
    370                 375                 380

Leu Ile Val Pro Val Leu Leu Asp Ala Ala Val Pro Ala Tyr Asp Lys
385                 390                 395                 400

Ile Arg Val Leu Leu Leu Tyr Ile Leu Leu Arg Asn Gly Val Ser Glu
                405                 410                 415

Glu Asn Leu Ala Lys Leu Ile Gln His Ala Asn Val Gln Ala His Ser
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420 425 430

Ser Leu Ile Arg Asn Leu Glu Gln Leu Gly Gly Thr Val Thr Asn Pro
435 440 445

Gly Gly Ser Gly Thr Ser Ser Arg Leu Glu Pro Arg Glu Arg Met Glu
450 455 460

Pro Thr Tyr Gln Leu Ser Arg Trp Thr Pro Val Ile Lys Asp Val Met
465 470 475 480

Glu Asp Ala Val Glu Asp Arg Leu Asp Arg Asn Leu Trp Pro Phe Val
485 490 495

Ser Asp Pro Ala Pro Thr Ala Ser Ser Gln Ala Ala Val Ser Ala Arg
500 505 510

Phe Gly His Trp His Lys Asn Lys Ala Gly Ile Glu Ala Arg Ala Gly
515 520 525

Pro Arg Leu Ile Val Tyr Val Met Gly Gly Val Ala Met Ser Glu Met
530 535 540

Arg Ala Ala Tyr Glu Val Thr Arg Ala Thr Glu Gly Lys Trp Glu Val
545 550 555 560

Leu Ile Gly Ser Ser His Ile Leu Thr Pro Thr Arg Phe Leu Asp Asp
565 570 575

Leu Lys Ala Leu Asp Lys Lys Leu Glu Asp Ile Ala Leu Pro
580 585 590

<210> 79
<211> 1888
<212> DNA
<213> Homo sapiens

<220>
<223> Syntaxin binding protein 2

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<212> PRT
<213> Rattus norvegicus

<220>
<223> Alpha-internexin

<400> 80

Met	Ser	Phe	Gly	Ser	Glu	His	Tyr	Leu	Cys	Ser	Ala	Ser	Ser	Tyr	Arg
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Lys	Val	Phe	Gly	Asp	Gly	Ser	Arg	Leu	Ser	Ala	Arg	Leu	Ser	Gly	Pro
			20					25					30		
Gly	Ala	Ser	Gly	Ser	Phe	Arg	Ser	Gln	Ser	Leu	Ser	Arg	Ser	Asn	Val
		35					40					45			
Ala	Ser	Thr	Ala	Ala	Cys	Ser	Ser	Ala	Ser	Ser	Leu	Gly	Leu	Gly	Leu
	50					55					60				
Ala	Tyr	Arg	Arg	Leu	Pro	Ala	Ser	Asp	Gly	Leu	Asp	Leu	Ser	Gln	Ala
65					70					75					80
Ala	Ala	Arg	Thr	Asn	Glu	Tyr	Lys	Ile	Ile	Arg	Thr	Asn	Glu	Lys	Glu
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Gln	Leu	Gln	Gly	Leu	Asn	Asp	Arg	Phe	Ala	Val	Phe	Ile	Glu	Lys	Val
			100					105					110		
His	Gln	Leu	Glu	Thr	Gln	Asn	Arg	Ala	Leu	Glu	Ala	Glu	Leu	Ala	Ala
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Leu	Arg	Gln	Arg	His	Ala	Glu	Pro	Ser	Arg	Val	Gly	Glu	Leu	Phe	Gln
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Arg	Glu	Leu	Arg	Glu	Leu	Arg	Ala	Gln	Leu	Glu	Glu	Ala	Ser	Ser	Ala
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Arg	Ala	Gln	Ala	Leu	Leu	Glu	Arg	Asp	Gly	Leu	Ala	Glu	Glu	Val	Gln
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Arg	Leu	Arg	Ala	Arg	Cys	Glu	Glu	Glu	Ser	Arg	Gly	Arg	Glu	Gly	Ala
			180					185					190		
Glu	Arg	Ala	Leu	Lys	Ala	Gln	Gln	Arg	Asp	Val	Asp	Gly	Ala	Thr	Leu
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Ala Arg Leu Asp Leu Glu Lys Lys Val Glu Ser Leu Leu Asp Glu Leu
    210                 215                 220

Ala Phe Val Arg Gln Val His Asp Glu Glu Val Ala Glu Leu Leu Ala
225                 230                 235                 240

Thr Leu Gln Ala Ser Ser Gln Ala Ala Ala Glu Val Asp Val Ala Val
                245                 250                 255

Ala Lys Pro Asp Leu Thr Ser Ala Leu Arg Glu Ile Arg Ala Gln Tyr
            260                 265                 270

Glu Ser Leu Ala Ala Lys Asn Leu Gln Ser Ala Glu Glu Trp Tyr Lys
        275                 280                 285

Ser Lys Phe Ala Asn Leu Asn Glu Gln Ala Ala Arg Ser Thr Glu Ala
    290                 295                 300

Ile Arg Ala Ser Arg Glu Glu Ile His Glu Tyr Arg Arg Gln Leu Gln
305                 310                 315                 320

Ala Arg Thr Ile Glu Ile Glu Gly Leu Arg Gly Ala Asn Glu Ser Leu
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Glu Arg Gln Ile Leu Glu Leu Glu Glu Arg His Ser Ala Glu Val Ala
            340                 345                 350

Gly Tyr Gln Asp Ser Ile Gly Gln Leu Glu Ser Asp Leu Arg Asn Thr
        355                 360                 365

Lys Ser Glu Met Ala Arg His Leu Arg Glu Tyr Gln Asp Leu Leu Asn
    370                 375                 380

Val Lys Met Ala Leu Asp Ile Glu Ile Ala Ala Tyr Arg Lys Leu Leu
385                 390                 395                 400

Glu Gly Glu Glu Thr Arg Phe Ser Thr Ser Gly Leu Ser Ile Ser Gly
                405                 410                 415

Leu Asn Pro Leu Pro Asn Pro Ser Tyr Leu Leu Pro Pro Arg Ile Leu
            420                 425                 430

Ser Ser Thr Thr Ser Lys Val Ser Ser Ala Gly Leu Ser Leu Lys Lys
        435                 440                 445

Glu Glu Glu Glu Glu Glu Glu Glu Glu Glu Gly Ala Ser Lys Glu Val
    450                 455                 460

Thr Lys Lys Thr Ser Lys Val Gly Glu Ser Phe Glu Glu Thr Leu Glu
465                 470                 475                 480

Glu Thr Val Val Ser Thr Lys Lys Thr Glu Lys Ser Thr Ile Glu Glu
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Ile Thr Thr Ser Ser Ser Gln Lys Met
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<211> 4593
<212> DNA
<213> Rattus norvegicus

<220>
<223> Alpha-internexin

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<211> 320
<212> PRT
<213> Mus musculus

<220>
<223> Beta-sarcoglycan

<400> 82

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             20                  25                  30

Asn Val Asn Lys Glu His Asn Ser Asn Phe Lys Ala Gly Tyr Ile Pro
         35                  40                  45

Ile Asp Glu Asp Arg Leu His Lys Thr Gly Leu Arg Gly Arg Lys Gly
     50                  55                  60

Asn Leu Ala Ile Cys Val Ile Val Leu Leu Phe Ile Leu Ala Val Ile
 65                  70                  75                  80

Asn Leu Leu Ile Thr Leu Val Ile Trp Ala Val Ile Arg Ile Gly Pro
                 85                  90                  95

Asn Gly Cys Asp Ser Met Glu Phe His Glu Ser Gly Leu Leu Arg Phe
            100                 105                 110

Lys Gln Val Ser Asp Met Gly Val Ile His Pro Leu Tyr Lys Ser Thr
        115                 120                 125

Val Gly Gly Arg Arg Asn Glu Asn Leu Val Ile Thr Gly Asn Asn Gln
    130                 135                 140

Pro Ile Val Phe Gln Gln Gly Thr Thr Lys Leu Ser Val Glu Lys Asn
145                 150                 155                 160

Lys Thr Ser Ile Thr Ser Asp Ile Gly Met Gln Phe Phe Asp Pro Arg
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                    165                 170                 175

Thr His Asn Ile Leu Phe Ser Thr Asp Tyr Glu Thr His Glu Phe His
            180                 185                 190

Leu Pro Ser Gly Val Lys Ser Leu Asn Val Gln Lys Ala Ser Thr Glu
        195                 200                 205

Arg Ile Thr Ser Asn Ala Thr Ser Asp Leu Asn Ile Lys Val Asp Gly
    210                 215                 220

Arg Ala Ile Val Arg Gly Asn Glu Gly Val Phe Ile Met Gly Lys Thr
225                 230                 235                 240

Ile Glu Phe His Met Gly Gly Asp Val Glu Leu Lys Ala Glu Asn Ser
                245                 250                 255

Ile Ile Leu Asn Gly Thr Val Met Val Ser Pro Thr Arg Leu Pro Ser
            260                 265                 270

Ser Ser Ser Gly Asp Gln Ser Gly Ser Gly Asp Trp Val Arg Tyr Lys
        275                 280                 285

Leu Cys Met Cys Ala Asp Gly Thr Leu Phe Lys Val Gln Val Thr Gly
    290                 295                 300

His Asn Met Gly Cys Gln Val Ser Asp Asn Pro Cys Gly Asn Thr His
305                 310                 315                 320
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<210> 83
<211> 1237
<212> DNA
<213> Mus musculus

<220>
<223> Beta-sarcoglycan

<400> 83

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<210> 84
<211> 251
<212> PRT
<213> Homo sapiens

<220>
<223> CGI-78 protein

<400> 84

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Ala Phe Ala Leu Phe Leu Ile Thr Val Ala Gly Asp Pro Leu Arg Val
             20                  25                  30

Ile Ile Leu Val Ala Gly Ala Phe Phe Trp Leu Val Ser Leu Leu Leu
         35                  40                  45

Ala Ser Val Val Trp Phe Ile Leu Val His Val Thr Asp Arg Ser Asp
     50                  55                  60

Ala Arg Leu Gln Tyr Gly Leu Leu Ile Phe Gly Ala Ala Val Ser Val
 65                  70                  75                  80

Leu Leu Gln Glu Val Phe Arg Phe Ala Tyr Tyr Lys Leu Leu Lys Lys
                 85                  90                  95

Ala Asp Glu Gly Leu Ala Ser Leu Ser Glu Asp Gly Arg Ser Pro Ile
            100                 105                 110

Ser Ile Arg Gln Met Ala Tyr Val Ser Gly Leu Ser Phe Gly Ile Ile
        115                 120                 125

Ser Gly Val Phe Ser Val Ile Asn Ile Leu Ala Asp Ala Leu Gly Pro
    130                 135                 140

Gly Val Val Gly Ile His Gly Asp Ser Pro Tyr Tyr Phe Leu Thr Ser
145                 150                 155                 160

Ala Phe Leu Thr Ala Ala Ile Ile Leu Leu His Thr Phe Trp Gly Val
                165                 170                 175

Val Phe Phe Asp Ala Cys Glu Arg Arg Arg Tyr Trp Ala Leu Gly Leu
            180                 185                 190

Val Val Gly Ser His Leu Leu Thr Ser Gly Leu Thr Phe Leu Asn Pro
        195                 200                 205

Trp Tyr Glu Ala Ser Leu Leu Pro Ile Tyr Ala Val Thr Val Ser Met
    210                 215                 220

Gly Leu Trp Ala Phe Ile Thr Ala Gly Gly Ser Leu Arg Ser Ile Gln
225                 230                 235                 240

Arg Ser Ser Cys Val Arg Thr Asp Tyr Leu Asp
                245                 250
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<210> 85

<211> 1967
<212> DNA
<213> Homo sapiens

<220>
<223> CGI-78 protein

<400> 85
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<210> 86
<211> 885
<212> PRT
<213> Homo sapiens

<220>
<223> KIAA0143 protein

<400> 86
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Pro Pro Arg Pro Ser Asn Gly Arg His Gly Ala Val Gly Ala Pro Cys
35 40 45

Ala Ala Pro Leu Ser Leu Gly Ala Ala Ala Ser Ala Val Glu Ile Ala

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     50                  55                  60

Met Pro Thr Arg Val Cys Cys Cys Cys Ser Ala Leu Arg Pro Arg Tyr
 65                  70                  75                  80

Lys Arg Leu Val Asp Asn Ile Phe Pro Glu Asp Pro Lys Asp Gly Leu
                 85                  90                  95

Val Lys Thr Asp Met Glu Lys Leu Thr Phe Tyr Ala Val Ser Ala Pro
            100                 105                 110

Glu Lys Leu Asp Arg Ile Gly Ser Tyr Leu Ala Glu Arg Leu Ser Arg
        115                 120                 125

Asp Val Val Arg His Arg Ser Gly Tyr Val Leu Ile Ala Met Glu Ala
    130                 135                 140

Leu Asp Gln Leu Leu Met Ala Cys His Ser Gln Ser Ile Lys Pro Phe
145                 150                 155                 160

Val Glu Ser Phe Leu His Met Val Ala Lys Leu Leu Glu Ser Gly Glu
                165                 170                 175

Pro Lys Leu Gln Val Leu Gly Thr Asn Ser Phe Val Lys Phe Ala Asn
            180                 185                 190

Ile Glu Glu Asp Thr Pro Ser Tyr His Arg Arg Tyr Asp Phe Phe Val
        195                 200                 205

Ser Arg Phe Ser Ala Met Cys His Ser Cys His Ser Asp Pro Glu Ile
    210                 215                 220

Arg Thr Glu Ile Arg Ile Ala Gly Ile Arg Gly Ile Gln Gly Val Val
225                 230                 235                 240

Arg Lys Thr Val Asn Asp Glu Leu Arg Ala Thr Ile Trp Glu Pro Gln
                245                 250                 255

His Met Asp Lys Ile Val Pro Ser Leu Leu Phe Asn Met Gln Lys Ile
            260                 265                 270

Glu Glu Val Asp Ser Arg Ile Gly Pro Pro Ser Ser Pro Ser Ala Thr
        275                 280                 285

Asp Lys Glu Glu Asn Pro Ala Val Leu Ala Glu Asn Cys Phe Arg Glu
    290                 295                 300

Leu Leu Gly Arg Ala Thr Phe Gly Asn Met Asn Asn Ala Val Arg Pro
305                 310                 315                 320

Val Phe Ala His Leu Asp His His Lys Leu Trp Asp Pro Asn Glu Phe
                325                 330                 335

Ala Val His Cys Phe Lys Ile Ile Met Tyr Ser Ile Gln Ala Gln Tyr
            340                 345                 350

Ser His His Val Ile Gln Glu Ile Leu Gly His Leu Asp Ala Arg Lys
        355                 360                 365

Lys Asp Ala Pro Arg Val Arg Ala Gly Ile Ile Gln Val Leu Leu Glu
    370                 375                 380
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Ala Val Ala Ile Ala Ala Lys Gly Ser Ile Gly Pro Thr Val Leu Glu
385                 390                 395                 400

Val Phe Asn Thr Leu Leu Lys His Leu Arg Leu Ser Val Glu Phe Glu
                405                 410                 415

Ala Asn Asp Leu Gln Gly Gly Ser Val Gly Ser Val Asn Leu Asn Thr
            420                 425                 430

Ser Ser Lys Asp Asn Asp Glu Lys Ile Val Gln Asn Ala Ile Ile Gln
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His Thr Leu Asp Ile Ser Gln Leu Gly Asp Leu Gly Thr Arg Arg Ile
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Gln Ile Met Leu Leu Arg Ser Leu Leu Met Val Thr Ser Gly Tyr Lys
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Ala Lys Thr Ile Val Thr Ala Leu Pro Gly Ser Phe Leu Asp Pro Leu
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Glu Val Met His Asn Leu Met Asp Arg His Asp Asn Arg Ala Lys Leu
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Gln Lys Asn Tyr Glu Leu Leu Tyr Thr Ser Leu Ala Leu Ile Thr Ile
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Ala Leu Gln Asp Ser Ala Ile Ile Asn Glu Asp Asn Leu Pro Met Phe
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His Arg Cys Gly Ile Met Ala Leu Val Ala Ala Tyr Leu Asn Phe Val
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Ser Gln Met Ile Ala Val Pro Ala Phe Cys Gln His Val Ser Lys Val
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Ser	Gly	Lys	Leu	Ser	Gln	Glu	Leu	Asp	Phe	Val	Ser	His	Asn	Val	Arg
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Thr	Lys	Leu	Asp	Glu	Leu	Lys	Arg	Gln	Glu	Val	Ser	Arg	Leu	Arg	Met
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Gln Glu Thr Glu Ala Leu Gly Arg Ser Gln Asp Arg Leu Glu Ala Gln
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Lys Arg Glu Leu Gln Gln Ala Val Leu Gln Met Glu Gln Arg Lys Gln
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Gln Phe Arg Ala Asp Thr Gly Asp Ala Pro Val Pro Ala Pro Ala Gly
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<400> 91

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<213> Rattus norvegicus

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Phe	Leu	Phe	Phe	Cys	Gln	Leu	Phe	Thr	Leu	Thr	Lys	Gly	Gly	Arg	Phe
			85					90					95		
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<220>
<223> Cytoplasmic beta-actin

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Asp Met Glu Lys Ile Trp His His Thr Phe Tyr Asn Glu Leu Arg Val
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Ala Pro Glu Glu His Pro Val Leu Leu Thr Glu Ala Pro Leu Asn Pro
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Lys Ala Asn Arg Glu Lys Met Thr Gln Ile Met Phe Glu Thr Phe Asn
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Thr Pro Ala Met Tyr Val Ala Ile Gln Ala Val Leu Ser Leu Tyr Ala
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Ser Gly Arg Thr Thr Gly Ile Val Met Asp Ser Gly Asp Gly Val Thr
145                 150                 155                 160

His Thr Val Pro Ile Tyr Glu Gly Tyr Ala Leu Pro His Ala Ile Leu
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Arg Leu Asp Leu Ala Gly Arg Asp Leu Thr Asp Tyr Leu Met Lys Ile
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Leu Thr Glu Arg Gly Tyr Ser Phe Thr Thr Thr Ala Glu Arg Glu Ile
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Val Arg Asp Ile Lys Glu Lys Leu Cys Tyr Val Ala Leu Asp Phe Glu
    210                 215                 220

Gln Glu Met Ala Thr Ala Ala Ser Ser Ser Ser Leu Glu Lys Ser Tyr
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Glu Leu Pro Asp Gly Gln Val Ile Thr Ile Gly Asn Glu Arg Phe Arg
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Cys Pro Glu Ala Leu Phe Gln Pro Ser Phe Leu Gly Met Glu Ser Cys
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Gly Ile His Glu Thr Thr Phe Asn Ser Ile Met Lys Cys Asp Val Asp
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Ile Arg Lys Asp Leu Tyr Ala Asn Thr Val Leu Ser Gly Gly Thr Thr
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Met Tyr Pro Gly Ile Ala Asp Arg Met Gln Lys Glu Ile Thr Ala Leu
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Tyr Ser Val Trp Ile Gly Gly Ser Ile Leu Ala Ser Leu Ser Thr Phe
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<222> 3859
<223> n is a or g or c or t

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<220>
<223> Ly6/neurotoxin homolog

<400> 96

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Cys Phe Lys Pro Met Arg Cys Pro Ala Met Ala Thr Tyr Cys Met Thr
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Val Pro Ser Cys Phe Glu Thr Val Tyr Asp Gly Tyr Ser Lys His Ala
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<213> Rattus norvegicus

<220>
<223> Astrocytic phosphoprotein

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Ser Glu Lys Ser Glu Glu Ile Thr Thr Gly Ser Ala Trp Phe Ser Phe
35 40 45

Leu Glu Ser His Asn Lys Leu Asp Lys Asp Asn Leu Ser Tyr Ile Glu
50 55 60

His Ile Phe Glu Ile Ser Arg Arg Pro Asp Leu Leu Thr Met Val Val
65 70 75 80

Asp Tyr Arg Thr Arg Val Leu Lys Ile Ser Glu Glu Asp Glu Leu Asp
85 90 95

Thr Lys Leu Thr Arg Ile Pro Ser Ala Lys Lys Tyr Lys Asp Ile Ile
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Arg Gln Pro Ser Glu Glu Glu Ile Ile Lys Leu Ala Pro Pro Pro Lys
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Lys Ala
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<210> 99
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<212> DNA
<213> Rattus norvegicus

<220>
<223> Astrocytic phosphoprotein

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<220>
<223> PLIC-1

<400> 100

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Lys Thr Pro Lys Glu Lys Glu Glu Phe Ala Val Pro Glu Asn Ser Ser
         35                  40                  45

Val Gln Gln Phe Lys Glu Glu Ile Ser Lys Arg Phe Lys Ser His Ile
     50                  55                  60

Asp Gln Leu Val Leu Ile Phe Ala Gly Lys Ile Leu Lys Asp Gln Asp
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65 70 75 80

Thr Leu Ser Gln His Gly Ile His Asp Gly Leu Thr Val His Leu Val
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Ile Lys Thr Gln Asn Arg Pro Gln Asp Asn Ser Ala Gln Gln Thr Asn
100 105 110

Thr Thr Gly Asn Ser Val Thr Ser Ser Pro Ala Pro Asp Ser Asn Pro
115 120 125

Thr Ser Gly Pro Ala Ala Asn Ser Ser Phe Gly Leu Gly Gly Leu Gly
130 135 140

Gly Leu Ala Gly Leu Ser Ser Leu Gly Leu Asn Thr Thr Asn Phe Phe
145 150 155 160

Glu Leu Gln Ser Gln Met Gln Arg Gln Leu Leu Ser Asn Pro Glu Met
165 170 175

Met Val Gln Ile Met Glu Asn Pro Phe Val Gln Ser Met Leu Ser Asn
180 185 190

Pro Asp Leu Met Arg Gln Leu Ile Met Ala Asn Pro Gln Met Gln Gln
195 200 205

Leu Ile Gln Arg Asp Pro Glu Ile Ser His Met Leu Asn Asn Pro Asp
210 215 220

Ile Met Gly Gln Thr Leu Glu Leu Ala Arg Asn Pro Ala Met Met Gln
225 230 235 240

Glu Met Met Arg Asn Gln Asp Arg Ala Leu Ser Asn Val Glu Ser Ile
245 250 255

Arg Gly Gly Tyr Asn Ala Leu Arg Arg Met Tyr Thr Asp Ile Gln Glu
260 265 270

Pro Met Ile Asn Ala Ala Gln Glu Gln Phe Gly Gly Asn Pro Phe Gly
275 280 285

Ser Leu Val Ser Ser Pro Ser Ser Ala Glu Gly Thr Gln Pro Ser Arg
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Thr Glu Asn Arg Asp Pro Leu Pro Asn Pro Trp Ala Pro Gln Thr Pro
305 310 315 320

Gln Ser Ser Pro Ala Tyr Gly Ser Ser Gly Ser Thr Asn Asn Thr Val
325 330 335

Ser Thr Ser Gly Gly Asn Ala Thr Ser Thr Pro Ala Gly Gln Gly Thr
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Ser Gly Pro Lys Leu Val Pro Gly Ala Gly Gly Ser Met Phe Asn Thr
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Met Gln Asn Met Leu Ser Ala Pro Tyr Met Arg Ser Met Leu Gln Ser
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405 410 415

Leu Phe Ala Gly Asn Pro Gln Leu Gln Glu Gln Met Arg Gln Gln Leu
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Pro Thr Phe Leu Gln Gln Met Gln Asn Pro Asp Thr Leu Ser Ala Met
435 440 445

Ser Asn Pro Arg Thr Met Gln Ala Leu Leu Gln Ile Gln Gln Gly Leu
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Gln Thr Leu Ala Thr Glu Ala Pro Gly Leu Ile Pro Gly Phe Thr Pro
465 470 475 480

Gly Leu Ala Ala Gly Asn Ser Gly Gly Pro Ala Gly Thr Thr Ala Pro
485 490 495

Ser Thr Ala Pro Gly Glu Asp Thr Asn Pro Gln Gly Gly Ala Ala Glu
500 505 510

Pro Gly His Gln Gln Phe Ile Gln Gln Met Leu Gln Ala Leu Ala Gly
515 520 525

Val Asn Pro Gln Leu Gln Ser Pro Glu Val Arg Phe Gln Gln Gln Leu
530 535 540

Glu Gln Leu Ser Ala Met Gly Phe Leu Lys Arg Glu Pro Asn Leu Gln
545 550 555 560

Ala Leu Ile Ala Thr Gly Gly Asp Ile Asn Ala Ala Ile Glu Arg Leu
565 570 575

Leu Gly Ser Gln Pro Ser
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<211> 1843
<212> DNA
<213> Mus musculus

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<223> PLIC-1

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<212> PRT
<213> Rattus norvegicus

<220>
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<400> 102

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Gly Val Gly Asn Arg Arg Ser Gly Arg Gly Gly Ser Gly Ile Arg Ser
         35                  40                  45

Ser Arg Phe Glu Glu Asp Asp Gly Asp Val Ala Met Asn Asp Pro Gln
     50                  55                  60

Asp Gly Pro Arg Val Arg Phe Asn Pro Tyr Thr Thr Arg Pro Asn Arg
 65                  70                  75                  80

Arg Arg Asp Thr Trp His Asp Arg Asp Arg Ile His Val Thr Val Arg
                 85                  90                  95

Arg Asp Arg Ala Pro Gln Glu Arg Gly Gly Ala Gly Thr Ser Gln Asp
            100                 105                 110

Gly Thr Thr Lys Asn Trp Phe Lys Ile Thr Ile Pro Tyr Gly Lys Lys
        115                 120                 125

Tyr Asp Lys Met Trp Leu Leu Ser Met Ile Gln Ser Lys Cys Ser Val
    130                 135                 140

Pro Phe Asn Pro Ile Glu Phe His Tyr Glu Asn Thr Arg Ala His Phe
145                 150                 155                 160

Phe Val Glu Asn Ala Thr Thr Ala Ser Ala Leu Lys Ala Val Asn Tyr
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Lys Ile Gln Asp Arg Glu Asn Gly Arg Ile Ser Ile Ile Ile Asn Ser
            180                 185                 190
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Ser Ala Pro Pro Tyr Ile Val Gln Asn Glu Leu Lys Pro Glu Gln Val
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Glu Gln Leu Lys Leu Ile Met Ser Lys Arg Tyr Asp Gly Ser Gln Gln
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Ala Leu Asp Leu Lys Gly Leu Arg Ser Asp Pro Asp Leu Val Ala Gln
225                 230                 235                 240

Asn Ile Asp Val Val Leu Asn Arg Arg Gly Cys Met Ala Ala Ala Leu
                245                 250                 255

Arg Ile Ile Glu Glu Asn Ile Pro Glu Leu Leu Ser Leu Asn Leu Ser
            260                 265                 270

Asn Asn Arg Leu Tyr Lys Leu Asp Asp Met Ser Ser Ile Val Gln Lys
        275                 280                 285

Ala Pro Asn Leu Lys Ile Leu Asn Leu Ser Gly Asn Glu Leu Lys Ser
    290                 295                 300

Glu Trp Glu Leu Asp Lys Ile Lys Gly Leu Lys Leu Glu Glu Leu Trp
305                 310                 315                 320

Leu Asp Arg Asn Pro Met Cys Asp Thr Phe Leu Asp Gln Ser Thr Tyr
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Ile Ser Thr Ile Arg Glu Arg Phe Pro Lys Leu Leu Arg Leu Asp Gly
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His Glu Leu Pro Pro Pro Ile Ala Phe Asp Val Glu Ala Pro Thr Met
        355                 360                 365

Leu Pro Pro Cys Lys Gly Ser Tyr Phe Gly Thr Glu Asn Leu Lys Ser
    370                 375                 380

Leu Val Leu His Phe Leu Gln Gln Tyr Tyr Ala Ile Tyr Asp Ser Gly
385                 390                 395                 400

Asp Arg Gln Gly Leu Leu Asp Ala Tyr His Asp Gly Ala Cys Cys Ser
                405                 410                 415

Leu Ser Thr Pro Ser Asn Pro Gln Asn Pro Val Arg His Asn Leu Ala
            420                 425                 430

Lys Tyr Phe Asn Asp Ser Arg Asn Val Lys Lys Ile Lys Asp Thr Thr
        435                 440                 445

Thr Arg Phe Arg Leu Leu Lys His Thr Arg Leu Asn Val Val Ala Phe
    450                 455                 460

Leu Asn Glu Leu Pro Lys Thr His His Asp Val Asn Ser Phe Val Val
465                 470                 475                 480

Asp Ile Ser Ala Gln Thr Ser Thr Leu Leu Cys Phe Ser Val Asn Gly
                485                 490                 495

Val Phe Lys Glu Val Asp Gly Lys Ser Arg Asp Ser Leu Arg Ala Phe
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Thr Arg Thr Phe Ile Ala Val Pro Ala Ser Asn Ser Gly Leu Cys Ile
        515                 520                 525
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Thr Leu Ser Gln Glu Gln Gln Asp Met Leu Gln Ala Phe Ser Thr Gln
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Ser Gly Met Asn Leu Glu Trp Ser Gln Lys Cys Leu Gln Asp Asn Asn
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<212> DNA
<213> Rattus norvegicus

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<223> Heat shock cognate protein 70

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Gln Gly Asn Arg Thr Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu
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Asn Thr Val Phe Asp Ala Lys Arg Leu Ile Gly Arg Arg Phe Asp Asp
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Ala Val Val Gln Ser Asp Met Lys His Trp Pro Phe Met Val Val Asn
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Asp Ala Gly Arg Pro Lys Val Gln Val Glu Tyr Lys Gly Glu Thr Lys
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Ser Phe Tyr Pro Glu Glu Val Ser Ser Met Val Leu Thr Lys Met Lys
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Glu Ile Ala Glu Ala Tyr Leu Gly Lys Thr Val Thr Asn Ala Val Val
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Ala Gly Thr Ile Ala Gly Leu Asn Val Leu Arg Ile Ile Asn Glu Pro
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Ile Leu Thr Thr Glu Asp Gly Ile Phe Glu Val Lys Ser Thr Ala Gly
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Asp Glu Lys Gln Arg Asp Lys Val Ser Ser Lys Asn Ser Leu Glu Ser
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Tyr Ala Phe Asn Met Lys Ala Thr Val Glu Asp Glu Lys Leu Gln Gly
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Glu His Gln Gln Lys Glu Leu Glu Lys Val Cys Asn Pro Ile Ile Thr
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Lys Leu Tyr Gln Ser Ala Gly Gly Met Pro Gly Gly Met Pro Gly Gly
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<220>
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<220>
<223> Tau microtubule associated protein

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Gly Thr Ser Asn Ala Thr Arg Ile Pro Ala Lys Thr Thr Pro Ser Pro
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Lys Thr Pro Pro Gly Ser Gly Glu Pro Pro Lys Ser Gly Glu Arg Ser
        115                 120                 125

Gly Tyr Ser Ser Pro Gly Ser Pro Gly Thr Pro Gly Ser Arg Ser Arg
    130                 135                 140

Thr Pro Ser Leu Pro Thr Pro Pro Thr Arg Glu Pro Lys Lys Val Ala
145                 150                 155                 160

Val Val Arg Thr Pro Pro Lys Ser Pro Ser Ala Ser Lys Ser Arg Leu
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Gln Thr Ala Pro Val Pro Met Pro Asp Leu Lys Asn Val Arg Ser Lys
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Ile Gly Ser Thr Glu Asn Leu Lys His Gln Pro Gly Gly Gly Lys Val
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Gln Ile Ile Asn Lys Lys Leu Asp Leu Ser Asn Val Gln Ser Lys Cys
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Gly Ser Lys Asp Asn Ile Lys His Val Pro Gly Gly Gly Ser Val Gln
225                 230                 235                 240

Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser Lys Cys Gly
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Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gln Val Glu Val
            260                 265                 270

Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg Val Gln Ser Lys Ile Gly
        275                 280                 285

Ser Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn Lys Lys Ile
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Glu Thr His Lys Leu Thr Phe Arg Glu Asn Ala Lys Ala Lys Thr Asp
305                 310                 315                 320

His Gly Ala Glu Ile Val His Lys Ser Pro Val Val Ser Gly Asp Thr
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Ser Pro Arg His Leu Ser Asn Val Ser Ser Thr Gly Ser Ile Asp Met
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Val Asp Ser Pro Gln Leu Ala Thr Leu Ala Asp Glu Val Ser Ala Ser
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Leu Ala Lys Gln Gly Leu
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<213> Rattus norvegicus

<220>
<223> Tau microtubule associated protein

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<212> PRT
<213> Rattus norvegicus

<220>
<223> Schwann cell peripheral myelin

<400> 110

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Leu Leu Phe Ser Ser Leu Val Leu Ser Pro Thr Leu Ala Ile Val Val
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Tyr Thr Asp Arg Glu Val Tyr Gly Ala Val Arg Ser Gln Val Thr Leu
        35                  40                  45

His Cys Ser Phe Trp Ser Ser Glu Trp Val Ser Asp Asp Ile Ser Phe
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     50                  55                  60

Thr Trp Arg Tyr Gln Pro Glu Gly Gly Arg Asp Ala Ile Ser Ile Phe
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His Tyr Ala Lys Gly Gln Pro Tyr Ile Asp Glu Val Gly Thr Phe Lys
                 85                  90                  95

Glu Arg Ile Gln Trp Val Gly Asp Pro Ser Trp Lys Asp Gly Ser Ile
            100                 105                 110

Val Ile His Asn Leu Asp Tyr Ser Asp Asn Gly Thr Phe Thr Cys Asp
        115                 120                 125

Val Lys Asn Pro Pro Asp Ile Val Gly Lys Thr Ser Gln Val Thr Leu
    130                 135                 140

Tyr Val Phe Glu Lys Val Pro Thr Arg Tyr Gly Val Val Leu Gly Ala
145                 150                 155                 160

Val Ile Gly Gly Ile Leu Gly Val Val Leu Leu Leu Leu Leu Leu Phe
                165                 170                 175

Tyr Leu Ile Arg Tyr Cys Trp Leu Arg Arg Gln Ala Ala Leu Gln Arg
            180                 185                 190

Arg Leu Ser Ala Met Glu Lys Gly Lys Phe His Lys Ser Ser Lys Asp
        195                 200                 205

Ser Ser Lys Arg Gly Arg Gln Thr Pro Val Leu Tyr Ala Met Leu Asp
    210                 215                 220

His Ser Arg Ser Thr Lys Ala Ala Ser Glu Lys Lys Ser Lys Gly Leu
225                 230                 235                 240

Gly Glu Ser Arg Lys Asp Lys Lys
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<210> 111
<211> 1029
<212> DNA
<213> Rattus norvegicus

<220>
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<400> 111

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<210> 112
<211> 444
<212> PRT
<213> Rattus norvegicus

<220>
<223> Class 1 beta tubulin

<400> 112

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Gly Ala Lys Phe Trp Glu Val Ile Ser Asp Glu His Gly Ile Asp Pro
             20                  25                  30

Thr Gly Thr Tyr His Gly Asp Ser Asp Leu Gln Leu Asp Arg Ile Ser
         35                  40                  45

Val Tyr Tyr Asn Glu Ala Thr Gly Gly Lys Tyr Val Pro Arg Ala Ile
     50                  55                  60

Leu Val Asp Leu Glu Pro Gly Thr Met Asp Ser Val Arg Ser Gly Pro
 65                  70                  75                  80

Phe Gly Gln Ile Phe Arg Pro Asp Asn Phe Val Phe Gly Gln Ser Gly
                 85                  90                  95

Ala Gly Asn Asn Trp Ala Lys Gly His Tyr Thr Glu Gly Ala Glu Leu
            100                 105                 110

Val Asp Ser Val Leu Asp Val Val Arg Lys Glu Ala Glu Ser Cys Asp
        115                 120                 125

Cys Leu Gln Gly Phe Gln Leu Thr His Ser Leu Gly Gly Gly Thr Gly
    130                 135                 140

Ser Gly Met Gly Thr Leu Leu Ile Ser Lys Ile Arg Glu Glu Tyr Pro
145                 150                 155                 160

Asp Arg Ile Met Asn Thr Phe Ser Val Val Pro Ser Pro Lys Val Ser
                165                 170                 175

Asp Thr Val Val Glu Pro Tyr Asn Ala Thr Leu Ser Val His Gln Leu
            180                 185                 190

Val Glu Asn Thr Asp Glu Thr Tyr Cys Ile Asp Asn Glu Ala Leu Tyr
        195                 200                 205

Asp Ile Cys Phe Arg Thr Leu Lys Leu Thr Thr Pro Thr Tyr Gly Asp
    210                 215                 220

Leu Asn His Leu Val Ser Ala Thr Met Ser Gly Val Thr Thr Cys Leu
225                 230                 235                 240

Arg Phe Pro Gly Gln Leu Asn Ala Asp Leu Arg Lys Leu Ala Val Asn
                245                 250                 255
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Met Val Pro Phe Pro Arg Leu His Phe Phe Met Pro Gly Phe Ala Pro
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Leu Thr Ser Arg Gly Ser Gln Gln Tyr Arg Ala Leu Thr Val Pro Glu
275 280 285

Leu Thr Gln Gln Val Phe Asp Ala Lys Asn Met Met Ala Ala Cys Asp
290 295 300

Pro Arg His Gly Arg Tyr Leu Thr Val Ala Ala Val Phe Arg Gly Arg
305 310 315 320

Met Ser Met Lys Glu Val Asp Glu Gln Met Leu Asn Val Gln Asn Lys
325 330 335

Asn Ser Ser Tyr Phe Val Glu Trp Ile Pro Asn Asn Val Lys Thr Ala
340 345 350

Val Cys Asp Ile Pro Pro Arg Gly Leu Lys Met Ala Val Thr Phe Ile
355 360 365

Gly Asn Ser Thr Ala Ile Gln Glu Leu Phe Lys Arg Ile Ser Glu Gln
370 375 380

Phe Thr Ala Met Phe Arg Arg Lys Ala Phe Leu His Trp Tyr Thr Gly
385 390 395 400

Glu Gly Met Asp Glu Met Glu Phe Thr Glu Ala Glu Ser Asn Met Asn
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Glu Glu Asp Phe Gly Glu Glu Ala Glu Glu Glu Ala
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<210> 113
<211> 2346
<212> DNA
<213> Rattus norvegicus

<220>
<223> Class 1 beta tubulin

<400> 113
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<212> PRT
<213> Rattus norvegicus

<220>
<223> Heat shock protein 90

<400> 114

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		35					40					45			
Asp	Ala	Leu	Asp	Lys	Ile	Arg	Tyr	Glu	Ser	Leu	Thr	Asp	Pro	Ser	Lys
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Phe	Met	Glu	Ala	Leu	Gln	Ala	Gly	Ala	Asp	Ile	Ser	Met	Ile	Gly	Gln
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Ala Gly Gly Ser Phe Thr Val Arg Ala Asp His Gly Glu Pro Ile Gly
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Arg Gly Thr Lys Val Ile Leu His Leu Lys Glu Asp Gln Thr Glu Tyr
            180                 185                 190

Leu Glu Glu Arg Arg Val Lys Glu Val Val Lys Lys His Ser Gln Phe
        195                 200                 205

Ile Gly Tyr Pro Ile Thr Leu Tyr Leu Glu Lys Glu Arg Glu Lys Glu
    210                 215                 220

Ile Ser Asp Asp Glu Ala Glu Glu Glu Lys Gly Glu Lys Glu Glu Glu
225                 230                 235                 240

Asp Lys Glu Asp Glu Glu Lys Pro Lys Ile Glu Asp Val Gly Ser Asp
                245                 250                 255

Glu Glu Asp Asp Ser Gly Lys Asp Lys Lys Lys Lys Thr Lys Lys Ile
            260                 265                 270

Lys Glu Lys Tyr Ile Asp Gln Glu Glu Leu Asn Lys Thr Lys Pro Ile
        275                 280                 285

Trp Thr Arg Asn Pro Asp Asp Ile Thr Gln Glu Glu Tyr Gly Glu Phe
    290                 295                 300

Tyr Lys Ser Leu Thr Asn Asp Trp Glu Asp His Leu Ala Val Lys His
305                 310                 315                 320

Phe Ser Val Glu Gly Gln Leu Glu Phe Arg Ala Leu Leu Phe Ile Pro
                325                 330                 335

Arg Arg Ala Pro Phe Asp Leu Phe Glu Asn Lys Lys Lys Lys Asn Asn
            340                 345                 350

Ile Lys Leu Tyr Val Arg Arg Val Phe Ile Met Asp Ser Cys Asp Asp
        355                 360                 365

Leu Ile Pro Glu Tyr Leu Asn Phe Ile Arg Gly Val Val Asp Ser Glu
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Claims

1. Use of:

(a) an isolated gene sequence that is down-regulated in the spinal cord of a mammal in response to mechanistically distinct first and second models of neuropathic or central sensitization pain;
(b) an isolated gene sequence comprising a nucleic acid sequence of any of Tables I to VI;
(c) an isolated gene sequence having at least 80% sequence identity with a nucleic acid sequence of any of Tables I to VI;
(d) an isolated nucleic acid sequence that is hybridizable to any of the gene sequences according to (a), (b) or (c) under stringent hybridisation conditions;
(e) a recombinant vector comprising a gene sequence or nucleic acid sequence according to any one of (a) to (d);
(f) a host cell containing the vector according to (e);
(g) a non-human animal having in its genome an introduced gene sequence or nucleic acid sequence or a removed or down-regulated gene sequence or nucleic acid sequence according to any one of (a) to (d);
(h) an isolated polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence encoded by a nucleotide sequence according to any one of (a) to (d), or a polypeptide variant thereof

with sequential amino acid deletions from the C terminus and/or the N-terminus;
(i) an isolated polypeptide encoded by a nucleotide sequence according to any one of (a) to (d); or
(j) an isolated antibody that binds specifically to a polypeptide according to (h) or (i);

in the screening of compounds for the treatment of pain, or for the diagnosis of pain.

2. Use according to claim 1, wherein the isolated gene sequence is down-regulated both in response to streptozocin-induced diabetes and in response to surgical injury of a nerve leading to the spine.

3. Use according to claim 1 or 2 wherein the isolated gene sequence encodes a kinase.

4. Use according to claim 1, 2 or 3, wherein the isolated gene sequence encodes an expression product or fragment thereof of pyruvate kinase, M1 and M2 subunits (M24359 ; X97047; X56494).

5. Use according to claim 1 or 2, wherein the isolated gene sequence encodes an expression product or fragment thereof of a receptor.

6. Use according to claim 1, 2 or 5, wherein the isolated gene sequence encodes dopamine receptor D.sub.1 (I58000).

7. Use according to claim 1 or 2, wherein the isolated gene sequence encodes a transporter.

8. Use according to claim 1, 2 or 7, wherein the isolated gene sequence encodes differentiation-associated Na^+-dependent inorganic phosphate cotransporter (AF271235) or putative vacuolar assembly protein VSP41 gene (U87309).

9. Use according to claim 1 or 2, wherein the isolated gene sequence encodes a G-protein coupled receptor protein.

10. Use according to claim 1, 2 or 9, wherein the isolated gene sequence encodes Git1 (G-protein-coupled receptor kinase-interactor 1 ; GPCR kinase-associated ADP-ribosylation factor) (AF085693).

11. Use according to claim 1 or 2, wherein the isolated gene sequence encodes a DNA-binding protein.

12. Use according to claim 1, 2 or 11, wherein the isolated gene sequence encodes putative histone H3.3A (X91866 ; M11354).

13. Use according to claim 1 or 2, wherein the isolated gene sequence encodes a ligase.

14. Use according to claim 1, 2 or 13, wherein the isolated gene sequence encodes 3-Hydroxy 3-methylglutaryl coenzyme A synthase, cytosolic (X52625), acyl-CoA synthetase II, brain (D360666) famesyl diphosphate synthase (M34477), bendless protein (AB032739; E12457), fatty acid synthase (X62888), glutamine synthetase (EC 6.3.1.2) (M91652), or putative seryl-tRNA synthetase (X91257).

15. Use according to claim 1 or 2, wherein the isolated gene sequence encodes a lyase.

16. Use according to claim 1, 2 or 15, wherein the lyase is enolase, alpha alpha, non-neuronal (NNE) (X02610; X52379; M14328).

17. Use according to claim 1 or 2, wherein the isolated gene sequence encodes an oxidoreductase.

18. Use according to claim 1, 2 or 17, wherein the isolated gene sequence encodes aldose reductase, lens (AREC 11.1.21) (X05884) cytochrome-c oxidase I, mitochondrial (S79304), lactate dehydrogenase-B (LDH-B) (U07181; X51905; Y00711), putative cytochrome c oxidase VIB (EC 1.9.3.1) (X13923), putative NADH: ubiquinone oxidoreductase PGIV subunit (AF044953), putative succinate dehydrogenase flavoprotein (AF095938; AF171022), putative ubiquinol—cytochrome-c reductase (EC 1.10.2.2) core protein II (J04973) or stearoyl-coA desaturase 2 (AB032243; M26270).

19. Use according to claim 1 or 2, wherein the isolated sequence encodes a transferase.

20. Use according to claim 1, 2 or 19, wherein the isolated sequence encodes ribophorin I (X05300) or sulfotransferase-like protein (AF188699).

21. Use according to claim 1 or 2, wherein the isolated sequence encodes a hydrolase.

22. Use according to claim 1, 2 or 21, wherein the isolated sequence encodes ATP synthase, H+, alpha subunit, mitochondrial (EC 3.6.1.34) (X56133), F1F0 ATPase delta subunit (U00926), putative dihydropyrimidinase related protein (D78013), heat shock protein 90 (S45392; M18186; M16660), or putative ribonuclease III (AF116910).

23. Use according to claim 1 or 2, wherein the isolated sequence encodes myelin basic protein S (MBP S) (K00512), transferring (D38380), neurofilament, light molecular weight (NF-L) (AF031880), myelin-associated glycoprotein (MAG) (M16800; M31811), NF-M middle molecular weight neurofilament protein (M18628) neuro-degeneration associated- protein 1 (D32249), S-100 protein β-subunit (X01090), microtubule-associated protein 1b (Map 1b) (X60370; L06237), putative cdc 37 homolog (D26564), putative ras-related protein Rab-5c (U11293), putative gelsolin (J04953), Cd81 antigen (target of antiproliferative antibody 1) (U19894; X59047; M33680), Mobp81 (Myelin-associated/Oligo-dendrocytic basic protein 81) (X87900), syntaxin binding protein n-secl, sec1 homolog, A-internexin (M73049), putative β-sarcoglycan A3b (AB024921), CGI-78 protein (AF151835), KIAA0143 (D63477), septin 2 (D50918), Nucleobindin (Z36277), myelin protein SR13 (M69139; S55427), B-Actin, cytoplasmic (V01217; X03672), ly6/neurotoxin (Lynx1) homolog (AD141377), astrocytic phosphoprotein ; PFA 15 gene (AJ243949; X86694), PLIC-1 (AF177345), Nfx1 (tip associating protein (TAP) gene) (AF093139; AF093140), A-Crystallin B (U04320; M73741 ; M28638), heat shock-like protein 70 kD (X70065; U73744; Y00371), tau microtubule-associated protein (X79321), myelin, Schwann cell, Perioheral (P-0) (K03242), B-Tubulin class 1 (AB011679; X04663; AF14139), putative long-chain polyunsaturated fatty acid elongation enzyme (Helo1) or peptidylglycine alpha-amidating monooxygenase 1.

24. A non-human animal having in its genome an introduced gene sequence or a removed or down-regulated gene sequence, said sequence being down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitisation pain.

25. A non-human animal according to claim 24, wherein said gene sequence becomes down regulated both in response to streptozocin induced diabetes and in response to chronic constriction injury.

26. A non-human animal according to claim 24 or 25, wherein the introduced gene sequence is according to any of claims 1 to 23.

27. A non-human animal according to any one of claims 24 to 26 which is *C. elegans.*

28. A kit comprising;

(a) affinity peptide and/or ligand and/or substrate for an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal in response to a mechanistically distinct first and second models of neuropathic or central sensitization pain ; and

(b) a defined quantity of an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal both in response to first and second models of neuropathic or central sensitization pain,
for simultaneous, separate or sequential use in detecting and/or quantifying down-regulation of a gene sequence in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain.

29. A kit according to claim 28, wherein the gene sequence is defined in any one of claims 1 to 23.

30. A kit comprising:

(a) nucleic acid sequences capable of hybridization to a nucleic acid sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain; and
(b) a defined quantity of one or more nucleic acid sequences capable of hybridization to a nucleic acid sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain,

for simultaneous, separate or sequential use in detecting and/or quantifying down-regulation of a gene sequence in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain.

31. The kit of claim 30, wherein the gene sequence is according to any of claims 1 to 23.

32. A compound that modulates the action of an expression product of a gene sequence that is down-regulated in the spinal cord of a mammal in response to first and second models of neuropathic or central sensitization pain.

33. A compound according to claim 32 wherein the gene sequence is listed in Tables I to VI.

34. A compound according to claim 32 or 33 wherein the nucleotide sequence is according to any one of claims 1 to 23.

35. A compound according to any one of claims 32 to 34 for use as a medicament.

36. A compound according to any one of claims 32 to 35 for the treatment or diagnosis of pain.

37. A pharmaceutical composition comprising a compound according to any one of claims 32 to 36 and a pharmaceutically acceptable carrier or diluent.

38. Use of a compound according to any one of claims 32 to 36 in the manufacture of a medicament for the treatment or diagnosis of pain.

39. Use of a compound according to any one of claims 32 to 36 in the manufacture of a medicament for the treatment or diagnosis of chronic pain.

40. A method of treatment of pain, which comprises administering to a patient an effective amount of a compound according to any one of claims 32 to 36.

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(54) Identification and use of molecules implicated in pain

(57) The invention relates to the use of:

(a) an isolated gene sequence that is down-regulated in the spinal cord of a mammal in response to mechanistically distinct first and second models of neuropathic or central sensitization pain;
(b) an isolated gene sequence comprising a nucleic acid sequence of any of Tables I to VI;
(c) an isolated gene sequence having at least 80% sequence identity with a nucleic acid sequence of any of Tables I to VI;
(d) an isolated nucleic acid sequence that is hybridizable to any of the gene sequences according to (a), (b) or (c) under stringent hybridisation conditions;
(e) a recombinant vector comprising a gene sequence or nucleic acid sequence according to any one of (a) to (d);
(f) a host cell containing the vector according to (e);
(g) a non-human animal having in its genome an introduced gene sequence or nucleic acid sequence or a removed or down-regulated gene sequence or nucleic acid sequence according to any one of (a) to (d);
(h) an isolated polypeptide comprising an amino acid sequence at least 90% identical to an amino acid sequence encoded by a nucleotide sequence according to any one of (a) to (d), or a variant polypeptide thereof with sequential amino acid deletions from the C terminus and/or the N-terminus;
(i) an isolated polypeptide encoded by a nucleotide sequence according to any one of (a) to (d); or
(j) an isolated antibody that binds specifically to a polypeptide according to (h) or (i);

in the screening of compounds for the treatment of pain, or for the diagnosis of pain.

The invention also relates to the use of naturally occurring compounds such as peptide ligands of the expression products of the above gene sequences and their associated signal transduction pathways for use in the treatment of pain.

EP 1 284 298 A3

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 02 25 5229

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	SHAH B ET AL: "Beta3, An auxiliary subunit of the voltage gated sodium channel is upr" SOCIETY FOR NEUROSCIENCE ABSTRACTS, SOCIETY FOR NEUROSCIENCE, US, vol. 26, no. 1-2, 4 November 2000 (2000-11-04), page 938,ABSTRACTNO3526, XP009020087 ISSN: 0190-5295 * the whole document * -----	1-3, 24-31	C12Q1/68 C07K14/47 C12N5/10 C12N15/85
Y	BITAR MILAD S ET AL: "Attenuation of IGF-1 antinociceptive action and a reduction in spinal cord gene expression of its receptor in experimental diabetes" PAIN, vol. 75, no. 1, March 1998 (1998-03), pages 69-74, XP002262337 ISSN: 0304-3959 * the whole document * ----- -/--	1-3, 24-31	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C12Q
C07K
C12N

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
Munich	3 December 2003	Hermann, P

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C37)

European Patent Office

INCOMPLETE SEARCH SHEET C

Application Number
EP 02 25 5229

The following comments apply to the invention for which a search has been performed - i.e. claims 1, 2, 24-40 (in part) and 3-4 (in full) relating to the first invention of the application.

The applicant should therefore bear in mind that, should he pay additional search fees, further objections leading to incomplete search might as well arise during the search phase of the further inventions.

Claim(s) searched completely:
2-4, 26

Claim(s) searched incompletely:
1, 24, 25, 27-31

Claim(s) not searched:
32-40

Reason for the limitation of the search:

a) Article 52 (4) EPC - Method for treatment of the human or animal body by therapy (claim 40).

Although claim 40 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search could have been been carried out and based on the alleged effects of the compound/composition. However, in view of the lack of clarity of said claim (see item (f) hereinbelow) no search has been carried out.

b) The isolated gene sequence of part (a) of claim 1 is only defined by a result achieved in special conditions, and the description is silent as to any other characteristic features pertaining to said isolated gene sequence. Claim 1 therefore lacks clarity (Article 84 EPC), and could only be searched as it relates to the isolated gene sequences of table I encoding a kinase, and derivative thereof as listed in parts (c)-(j) of claim 1, all relating to kinase encoding nucleic acid sequences.

c)The non-human animal of present claims 24 or 25 or the C. elegans of claim 27 is defined by reference to the following parameter:

- the modification of the presence or expression of a gene sequence which is downregulated in the spinal cord of a mammal in response to two models of neuropathic pain and claim 25, as for it, limits those two models to the streptozocin induced-diabetes and the chronic constriction injury.

The use of that parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC (see also Guidelines C-III, 4.7a). For the same reasons as those hereinabove under item (b), the search for claims 24, 25 and 27 has been restricted to

European Patent Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 02 25 5229

non-human animal wherein the introduced gene sequence is one of the sequences listed in Table I, encoding a kinase.

d) The expression product of a gene sequence and the nucleic acid sequence of the kits of claims 28-31 are only defined by a parameter - i.e. the expression product of said gene sequence or the nucleic acid sequence that is downregulated in the spinal cord of a mammal in response to two models of neuropathic pain. The use of that parameter in the present context is considered to lead to a lack of clarity within the meaning of Article 84 EPC (see also Guidelines C-III, 4.7a). For the same reasons as those hereinabove under item (b), the search for claims 28-31 has been restricted respectively to the product of the gene sequences given in Table I and to the sequences given in Table I themselves.

e) Moreover in independent claim 28 none of the characteristic features of the "affinity peptide", "ligand" and "substrate" for the expression product are given in said claim, and the description is also silent as to said eventual characteristics. Therefore the skilled person would not clearly understand which compounds are falling under the scope of said claim. Said claim therefore lacks clarity (Article 84 EPC) to such an extent that a meaningful search on its entire scope could not be performed. Said search has been restricted to substrates known for the kinases encoded by the gene sequences listed in table I.

f) Claims 32-36 relate to compounds only defined by the result to be achieved and the claims as well as the description do not relate to any features which would allow the skilled person to clearly understand which compounds are falling under the scope of said claims. Said claims therefore lack clarity (Article 84 EPC) to such an extent that no meaningful search could be performed.

As claims 37-40 are depending upon one or more of claims 32-36, said claims therefore lack clarity (Article 84 EPC) and could not be searched either.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 25 5229

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	BLACKBURN-MUNRO G ET AL: "The sodium channel auxiliary subunits beta1 and beta2 are differentially expressed in the spinal cord of neuropathic rats" NEUROSCIENCE, vol. 90, no. 1, April 1999 (1999-04), pages 153-164, XP002262713 ISSN: 0306-4522 * the whole document *	1-3, 24-31	
A	NAKAMURA JIRO ET AL: "A protein kinase C-beta-selective inhibitor ameliorates neural dysfunction in streptozotocin-induced diabetic rats" DIABETES, vol. 48, no. 10, October 1999 (1999-10), pages 2090-2095, XP002260473 ISSN: 0012-1797 * the whole document *	1-3, 24-31	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A	LUO Z DAVID ET AL: "Neuronal nitric oxide synthase mRNA upregulation in rat sensory neurons after spinal nerve ligation: Lack of a role in allodynia development" JOURNAL OF NEUROSCIENCE, vol. 19, no. 21, 1 November 1999 (1999-11-01), pages 9201-9208, XP002262714 ISSN: 0270-6474 * the whole document *	1-3, 24-31	

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EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 25 5229

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	FOX ALYSON ET AL: "Critical evaluation of the streptozotocin model of painful diabetic neuropathy in the rat" PAIN, vol. 81, no. 3, June 1999 (1999-06), pages 307-316, XP002260439 ISSN: 0304-3959 * the whole document *	1-3, 24-31	
A	COURTEIX C ET AL: "Streptozocin-induced diabetic rats: Behavioural evidence for a model of chronic pain" PAIN, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 53, no. 1, 1993, pages 81-88, XP009020332 ISSN: 0304-3959 * the whole document *	1-3, 24-31	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A	MALMBERG ANNIKA B ET AL: "Preserved acute pain and reduced neuropathic pain in mice lacking PKC-gamma" SCIENCE (WASHINGTON D C), vol. 278, no. 5336, 1997, pages 279-283, XP002260438 ISSN: 0036-8075 * the whole document *	1-3, 24-31	
A	WO 00/63427 A (CUVILLIER GWLADYS ;DEVGEN NV (BE); BOGAERT THIERRY (BE); PLATTEEUW) 26 October 2000 (2000-10-26) * the whole document *	1-3, 24-31	
	-/--		

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 02 25 5229

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	TAO Y -X ET AL: "Expression and action of cyclic GMP-dependent protein kinase Ialpha in inflammatory hyperalgesia in rat spinal cord" NEUROSCIENCE, vol. 95, no. 2, 1 December 2000 (2000-12-01), pages 525-533, XP002260437 ISSN: 0306-4522 * the whole document *	1-3, 24-31	
A	BRIDGES D ET AL: "MECHANISMS OF NEUROPATHIC PAIN" BRITISH JOURNAL OF ANAESTHESIA, BJM PUBLISHING GROUP, LONDON, GB, vol. 87, no. 1, 2001, pages 12-26, XP001068882 ISSN: 0007-0912 * the whole document *	1-3, 24-31	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
T	CIRUELA A ET AL: "Identification of MEK1 as a novel target for the treatment of neuropathic pain." BRITISH JOURNAL OF PHARMACOLOGY, vol. 138, no. 5, March 2003 (2003-03), pages 751-756, XP002260445 ISSN: 0007-1188 (ISSN print) * the whole document *	1-3, 24-31	

EPO FORM 1503 03.82 (P04C10)

European Patent Office

Application Number
EP 02 25 5229

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☒ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

1, 2, 24-40 (in part) 3-4 (in full)

European Patent Office

LACK OF UNITY OF INVENTION SHEET B

Application Number
EP 02 25 5229

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Invention 1: 1, 2, 24-40 (in part) 3-4 (in full)

Invention 1 relates to: i) the use of an isolated gene sequence encoding a kinase according to Table I, or derivative thereof such as recombinant vector, host cells or non-human animal comprising said isolated gene sequence, or isolated polypeptide encoded by, or comprising an isolated polypeptide encoded by said isolated gene sequence or isolated antibody directed against the above cited polypeptides, in the screening of compounds for the treatment of pain, or for the diagnosis of pain; ii) a non-human animal having introduced in its genome, said isolated gene sequence; iii) kits comprising either the expression product of said isolated gene sequence and its substrate, ligand or affinity peptide; iv) a compound that modulates the action of the expression product of said selected gene sequence; v) a pharmaceutical composition comprising said compound; vi) the use of said compound for the treatment or the diagnosis of pain; and vii) a method of treatment of pain which comprises administering to a patient an effective amount of said compound.

Invention 2: 1, 2, 24-40 (in part) 5-6 (in full)

Invention 2 is equivalent to invention 1 for an isolated gene sequence encoding an expression product or a fragment thereof of a receptor according to Table II.

Invention 3: 1, 2, 24-40 (in part) 7-8 (in full)

Invention 3 is equivalent to invention 1 for an isolated gene sequence encoding a transporter according to Table III.

Invention 4: 1, 2, 24-40 (in part) 9-10 (in full)

Invention 4 is equivalent to invention 1 for an isolated gene sequence encoding a G-protein coupled receptor protein according to Table IV.

Invention 5: 1, 2, 24-40 (in part) 11-12 (in full)

Invention 5 is equivalent to invention 1 for an isolated gene sequence encoding a DNA-binding protein according to Table V.

Invention 6: 1, 2, 24-40 (in part) 13-14 (in full)

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 02 25 5229

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Invention 6 is equivalent to invention 1 for an isolated gene sequence encoding a ligase according to rows 1-7 of Table VI.

Invention 7: 1, 2, 24-40 (in part) 15-16 (in full)

Invention 7 is equivalent to invention 1 for an isolated gene sequence encoding a lyase according to row 8 of Table VI.

Invention 8: 1, 2, 24-40 (in part) 17-18 (in full)

Invention 8 is equivalent to invention 1 for an isolated gene sequence encoding an oxido-reductase according to rows 9-16 of Table VI.

Invention 9: 1, 2, 24-40 (in part) 19-20 (in full)

Invention 9 is equivalent to invention 1 for an isolated gene sequence encoding a transferase according to rows 17-18 of Table VI.

Invention 10: 1, 2, 24-40 (in part) 21-22 (in full)

Invention 10 is equivalent to invention 1 for an isolated gene sequence encoding a hydrolase according to rows 19-21 and 54 of Table VI.

Invention 11: 1, 2, 23-40 (in part)

Invention 11 is equivalent to invention 1 for an isolated gene sequence encoding a protein according to 23rd row of Table VI.

Inventions 12-41: 1, 2, 23-40 (in part)

Inventions 12-41 are equivalent to invention 1 for an isolated gene sequences encoding a protein according to the 24th-53rd rows of Table VI respectively.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 02 25 5229

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

03-12-2003

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		US 2003149995 A1	07-08-2003
		US 6540996 B1	01-04-2003

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82